5-HT_{2B} RECEPTOR ANTAGONISTS

This invention relates to 5-HT_{2B} receptor antagonists, pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions to treat various diseases.

Background to the invention

Serotonin, also referred to as 5-hydroxytryptamine (5-HT), is a neurotransmitter with mixed and complex pharmacological characteristics. 5-HT acts via a number of discrete 5-HT receptors. Currently, fourteen subtypes of serotonin receptor are recognised and delineated into seven families, 5-HT_1 to 5-HT_7. Within the 5-HT_2 family, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} subtypes are known to exist. The nomenclature and classification of 5-HT receptors has been reviewed by Martin and Humphrey, *Neuropharm.*, 33, 261-273 (1994) and Hoyer, *et al.*, *Pharm. Rev.*, 46, 157-203 (1994).

There is evidence to suggest a role for 5-HT_{2B} receptors in a number of medical disorders, and therefore 5-HT_{2B} receptor antagonists are likely to have a beneficial effect on patients suffering these disorders. They include, but are not limited to: disorders of the GI tract, and especially disorders involving altered motility, and particularly irritable bowel syndrome (WO 01/08668); disorders of gastric motility, dyspepsia, GERD, tachygastria; migraine/neurogenic pain (WO 97/44326); pain (US 5 958 934); anxiety (WO 97/44326); depression (WO 97/44326); benign prostatic hyperplasia (US 5 952 331); sleep disorder (WO 97/44326); panic disorder, obsessive compulsive disorder, alcoholism, hypertension, anorexia nervosa, and priapism (WO 97/44326); asthma and obstructive airway disease (US 5 952 331);

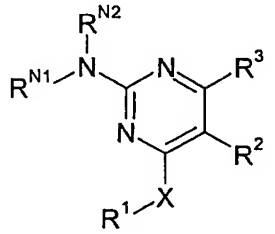
incontinence and bladder dysfunction (WO 96/24351); disorders of the uterus, such as dysmenorrhoea, pre-term labour, post-partum remodelling, endometriosis and fibrosis; pulmonary hypertension (Launay, J.M., *et al.*, *Nature Medicine*, **8(10)**, 1129-1135 (2002)).

WO 97/44326 describes aryl pyrimidine derivatives and their use as selective 5-HT_{2B} antagonists. However, although this application discloses a number of compounds, it is desirable to find further classes of compounds to act as 5-HT_{2B} antagonists, which are preferably selective against 5-HT_{2A} and 5-HT_{2C} receptors.

The present inventors have previously described such compounds in co-pending applications PCT/GB2003/000567 and PCT/GB2003/000552, filed 11 February 2003 and US 10/364,672, filed 12 February 2003, which are all incorporated herein by reference.

Summary of the invention

A first aspect of the present invention provides the use of a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a condition alleviated by antagonism of a 5-HT_{2B} receptor,

wherein:

X is O or NH;

R^2 and R^3 are independently selected from the group

consisting of H, and optionally substituted C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, and phenyl-C_{1-4} alkyl;
R^1 is an optionally substituted C_{9-14} aryl group or an optionally substituted C_{5-7} aryl group (which includes an optionally substituted bi-C_{5-7} aryl group);
R^{N1} and R^{N2} are either:
(i) independently selected from H, R, R', SO_2R, C(=O)R, $(CH_2)_nNR^{N3}R^{N4}$, where n is from 1 to 4 and R^{N3} and R^{N4} are independently selected from H and R, where R is optionally substituted C_{1-4} alkyl, and R' is optionally substituted phenyl-C_{1-4} alkyl, or
(ii) together with the nitrogen atom to which they are attached, form an optionally substituted C_{5-7} heterocyclic group.

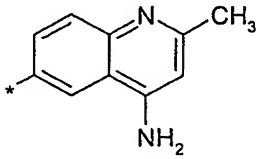
A second aspect of the present invention provides a method of treating a condition which can be alleviated by antagonism of a 5-HT_{2B} receptor, which method comprises administering to a patient in need of treatment an effective amount of a compound of formula I as defined in the first aspect, or a pharmaceutically acceptable salt thereof.

Conditions which can be alleviated by antagonism of a 5-HT_{2B} receptor are discussed above, and particularly include disorders of the GI tract.

A third aspect of the present invention provides the use of a compound of formula I as defined in the first aspect or a pharmaceutically acceptable salt thereof in a method of therapy, with the proviso that when R^{N1}, R^{N2} and R^2 are H, R^3 is methyl, and X is NH, then R^1 is not: phenyl; 3-I, 4-Me-phenyl; 3,5-diacetyl-phenyl, 3-acetyl-phenyl; 4-acetyl-phenyl; and 2-carboxy-phenyl.

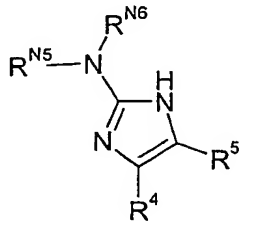
A fourth aspect of the present invention provides a pharmaceutical composition comprising a compound of formula I as defined in the first aspect or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent, with the proviso that when R^{N1}, R^{N2} and R^2 are H, R^3 is methyl, and X is NH, then R^1 is not: phenyl; 3-I, 4-Me-phenyl; 3,5-diacetyl-phenyl, 3-acetyl-phenyl; 4-acetyl-phenyl; and 2-carboxy-phenyl.

A fifth aspect of the present invention provides a compound of formula I as defined in the first aspect, except that R^1 can be an optionally substituted C_{9-14} aryl group or an optionally substituted bi-C_{5-7} aryl group, or a salt, solvate and chemically protected form thereof, with the proviso that when R^{N1}, R^{N2} and R^2 are H, R^3 is methyl, and X is NH, then R^1 is not:



It is preferred that the compounds described above are selective as against 5-HT_{2A} and 5-HT_{2C} receptors.

A sixth aspect of the present invention provides the use of a compound of formula II:



(II)

or a pharmaceutically acceptable salt thereof, in the

preparation of a medicament for the treatment of a condition alleviated by antagonism of a 5-HT_{2B} receptor,
wherein:
R^5 is selected from the group consisting of H, and optionally substituted C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, and phenyl-C_{1-4} alkyl;
R^4 is an optionally substituted C_{9-14} aryl group or an optionally substituted bi-C_{5-7} aryl group;
R^{N5} and R^{N6} are either:
(i) independently selected from H, R, R', SO_2R, C(=O)R, $(CH_2)_nNR^{N7}R^{N8}$, where n is from 1 to 4 and R^{N7} and R^{N8} are independently selected from H and R, where R is optionally substituted C_{1-4} alkyl, and R' is optionally substituted phenyl-C_{1-4} alkyl, or
(ii) together with the nitrogen atom to which they are attached, form an optionally substituted C_{5-7} heterocyclic group.

A seventh aspect of the present invention provides a method of treating a condition which can be alleviated by antagonism of a 5-HT_{2B} receptor, which method comprises administering to a patient in need of treatment an effective amount of a compound of formula II as defined in the sixth aspect, or a pharmaceutically acceptable salt thereof.

Conditions which can be alleviated by antagonism of a 5-HT_{2B} receptor are discussed above, and particularly include disorders of the GI tract.

An eighth aspect of the present invention provides the use of a compound of formula II as defined in the sixth aspect, with the proviso that when R^{N5}, R^{N6} and R^5 are H, R^4 is not unsubstituted 2-naphthyl or unsubstituted 4-phenyl-phenyl,

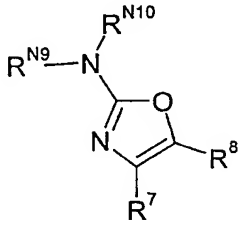
or a pharmaceutically acceptable salt thereof, in a method of therapy.

A ninth aspect of the present invention provides a pharmaceutical composition comprising a compound of formula II as defined in the eigth aspect or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

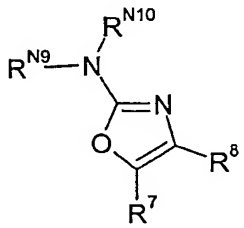
A tenth aspect of the present invention provides a compound of formula II as defined in the sixth aspect or a salt, solvate and chemically protected form thereof, with the proviso that when R^{N5}, R^{N6} and R^5 are H, R^4 is not unsubstituted 1- or 2-naphthyl or unsubstituted 4-phenyl-phenyl.

It is preferred that the compounds described above are selective as against 5-HT_{2A} and 5-HT_{2C} receptors.

An eleventh aspect of the present invention provides the use of a compound of formula IIIa or IIIb:



(IIIa)



(IIIb)

or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a condition alleviated by antagonism of a 5-HT_{2B} receptor, wherein:
R^8 is selected from the group consisting of H, and optionally substituted C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, and phenyl-C_{1-4} alkyl;
R^7 is an optionally substituted bi-C_{5-7} aryl group;

R^{N9} and R^{N10} are either:
(i) independently selected from H, R, R', SO_2R, C(=O)R, $(CH_2)_nNR^{N11}R^{N12}$, where n is from 1 to 4 and R^{N11} and R^{N12} are independently selected from H and R, where R is optionally substituted C_{1-4} alkyl, and R' is optionally substituted phenyl-C_{1-4} alkyl, or
(ii) together with the nitrogen atom to which they are attached, form an optionally substituted C_{5-7} heterocyclic group.

A twelth aspect of the present invention provides a method of treating a condition which can be alleviated by antagonism of a 5-HT_{2B} receptor, which method comprises administering to a patient in need of treatment an effective amount of a compound of formula I as defined in the eleventh aspect, or a pharmaceutically acceptable salt thereof.

Conditions which can be alleviated by antagonism of a 5-HT_{2B} receptor are discussed above, and particularly include disorders of the GI tract.

A thirteenth aspect of the present invention provides the use of a compound of formula IIIa or IIIb as defined in the eleventh aspect, or a pharmaceutically acceptable salt thereof, in a method of therapy.

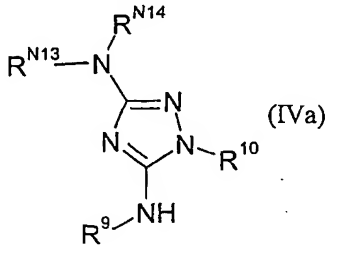
A fourteenth aspect of the present invention provides a pharmaceutical composition comprising a compound of formula IIIa or IIIb as defined in the eleventh aspect, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

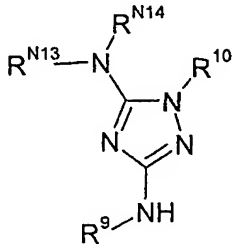
A fifteenth aspect of the present invention provides a

compound of formula IIIa or IIIb as defined in the eleventh aspect, or a salt, solvate and chemically protected form thereof, with the proviso that in formula IIIb, when R^{N9}, R^{N10} and R^8 are H, R^7 is not 4-phenyl-phenyl.

It is preferred that the compounds described above are selective as against 5-HT_{2A} and 5-HT_{2C} receptors.

A sixteenth aspect of the present invention provides a compound of formula IVa or IVb:


(IVa)


(IVb)

or a salt, solvate and chemically protected form thereof, wherein:

R^{10} is selected from the group consisting of H and optionally substituted C_{1-6} alkyl;

R^9 is an optionally substituted C_{9-14} aryl group or an optionally substituted bi-C_{5-7} aryl group;

R^{N13} and R^{N14} are either:

(i) independently selected from H, R, R', SO_2R, C(=O)R, $(CH_2)_nNR^{N15}R^{N16}$, where n is from 1 to 4 and R^{N15} and R^{N16} are independently selected from H and R, where R is optionally substituted C_{1-4} alkyl, and R' is optionally substituted phenyl-C_{1-4} alkyl, or

(ii) together with the nitrogen atom to which they are attached, form an optionally substituted C_{5-7} heterocyclic group.

A seventeenth aspect of the present invention provides the

use of a compound of formula IVa or IVb as defined in the sixteenth aspect or a pharmaceutically acceptable salt thereof in a method of therapy.

An eighteenth aspect of the present invention provides a pharmaceutical composition comprising a compound of formula IVa or IVb as defined in the sixteenth aspect or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

A ninteenth aspect of the present invention provides the use of a compound of formula IVa or IVb as defined in the sixteenth aspect or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by antagonism of a 5-HT_{2B} receptor.

A twentieth aspect of the present invention provides a method of treating a condition which can be alleviated by antagonism of a 5-HT_{2B} receptor, which method comprises administering to a patient in need of treatment an effective amount of a compound of formula IVa or IVb as defined in the sixteenth aspect, or a pharmaceutically acceptable salt thereof.

Conditions which can be alleviated by antagonism of a 5-HT_{2B} receptor are discussed above, and particularly include disorders of the GI tract.

It is preferred that the compounds described above are selective as against 5-HT_{2A} and 5-HT_{2C} receptors.

Definitions

C_{1-6} alkyl group: The term "C_{1-6} alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a non-cyclic hydrocarbon compound having from 1 to 6 carbon atoms, and which may be saturated or unsaturated.

Examples of saturated C_{1-6} alkyl groups include methyl (C_1); ethyl (C_2); propyl (C_3), which may be linear (n-propyl) or branched (iso-propyl); butyl (C_4), which may be linear (n-butyl) or branched (iso-butyl, sec-butyl and tert-butyl); pentyl (C_5), which may be linear (n-pentyl, amyl) or branched (iso-pentyl, neo-pentyl); hexyl (C_6), which may be linear (n-hexyl) or branched.

Examples of unsaturated C_{1-6} alkyl groups, which may be referred to as C_{1-6} alkenyl (if they included a double bond) or C_{1-6} alkynyl (if they include a triple bond) groups, include ethenyl (vinyl, $-CH=CH_2$), ethynyl (ethinyl, $-C\equiv CH$), 1-propenyl ($-CH=CH-CH_3$), 2-propenyl (allyl, $-CH-CH=CH_2$), 2-propynyl (propargyl, $-CH_2-C\equiv CH$), isopropenyl ($-C(CH_3)=CH_2$), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

C_{3-7} Cycloalkyl: The term "C_{3-7} cycloalkyl", as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 7 ring atoms

Examples of saturated cycloalkyl groups include, but are not limited to, those derived from: cyclopropane (C_3),

cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6), and cycloheptane (C_7).

Examples of unsaturated cylcoalkyl groups include, but are not limited to, those derived from: cyclobutene (C_4), cyclopentene (C_5), cyclohexene (C_6), and cycloheptene (C_7).

C_{3-7} cycloalkyl-C_{1-4} alkyl: The term "C_{3-7} cycloalkyl-C_{1-4} alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a non-cyclic hydrocarbon compound having from 1 to 4 carbon atoms (C_{1-4} alkyl), which may be saturated or unsaturated, which itself is substituted by a C_{3-7} cycloalkyl group.

Examples of C_{3-7} cycloalkyl-C_{1-4} alkyl groups include, but are not limited to, those derived from: cyclohexylethane (C_6-C_2) and cyclopentylpropene (C_5-C_3).

Phenyl-C_{1-4} alkyl: The term "phenyl-C_{1-4} alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a non-cyclic hydrocarbon compound having from 1 to 4 carbon atoms (C_{1-4} alkyl), which may be saturated or unsaturated, which itself is substituted by a phenyl group (C_6H_5-).

Examples of phenyl-C_{1-4} alkyl groups include, but are not limited to, benzyl (phenyl-CH_2-) and those derived from: phenylethane (phenyl-C_2) and phenylpropene (phenyl-C_3).

C_{5-7} Heterocyclyl: The term "C_{5-7} heterocyclyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 5 to 7 ring atoms, of which from 1 to

4 are ring heteroatoms. In particular, when R^2 and R^3 together with the nitrogen atom to which they are attached form a C_{5-7} heterocyclic ring, at least one ring atom will be nitrogen.

Examples of C_{5-7} heterocyclyl groups having at least one nitrogen atom, include, but are not limited to, those derived from:
GN_1: pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);
N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);
N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);
N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);
N_2O_1: oxadiazine (C_6);
$N_1O_1S_1$: oxathiazine (C_6).

C_{9-14} Aryl: The term "C_{9-14} aryl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound with at least two fused rings, which moiety has from 9 to 14 ring atoms. Preferably, each ring has from 5 to 7 ring atoms.

The ring atoms may be all carbon atoms, as in "carboaryl groups" (e.g. C_{9-14} carboaryl).

Examples of carboaryl groups include, but are not limited to, those derived from naphthalene (C_{10}), azulene (C_{10}), anthracene (C_{14}) and phenanthrene (C_{14}).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C_9), isoindene (C_9) tetralin (C_{10}) and fluorene (C_{13}).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups" (e.g. C_{9-14} heteroaryl).

Examples of heteroaryl groups, include, but are not limited to:

C_9 heteroaryl groups (with 2 fused rings) derived from benzofuran (O_1), isobenzofuran (O_1), indole (N_1), isoindole (N_1), indolizine (N_1), indoline (N_1), isoindoline (N_1), purine (N_4) (e.g. adenine, guanine), benzimidazole (N_2), indazole (N_2), benzoxazole (N_1O_1), benzisoxazole (N_1O_1), benzodioxole (O_2), benzofurazan (N_2O_1), benzotriazole (N_3), benzothiophene (S_1), benzothiazole (N_1S_1), benzothiadiazole (N_2S);

C_{10} heteroaryl groups (with 2 fused rings) derived from chromene (O_1), isochromene (O_1), chroman (O_1), isochroman (O_1), benzodioxan (O_2), quinoline (N_1), isoquinoline (N_1), quinolizine (N_1), benzoxazine (N_1O_1), benzodiazine (N_2), pyridopyridine (N_2), quinoxaline (N_2), quinazoline (N_2), cinnoline (N_2), phthalazine (N_2), naphthyridine (N_2), pteridine (N_4);

C_{11} heteroaryl groups (with 2 fused rings) derived from benzoazepine (N_1), 5-oxa-9-aza-benzocycloheptene (N_1O_1);

C_{13} heteroaryl groups (with 3 fused rings) derived from carbazole (N_1), dibenzofuran (O_1), dibenzothiophene (S_1), carboline (N_2), perimidine (N_2), pyridoindole (N_2); and,

C_{14} heteroaryl groups (with 3 fused rings) derived from acridine (N_1), xanthene (O_1), thioxanthene (S_1), oxanthrene (O_2), phenoxathiin (O_1S_1), phenazine (N_2), phenoxazine (N_1O_1), phenothiazine (N_1S_1), thianthrene (S_2), phenanthridine (N_1), phenanthroline (N_2), phenazine (N_2).

The above described C_{9-14} aryl group includes the radical formed by removal of a hydrogen atom from any of the possible aromatic ring atoms. The groups formed by this removal can be described by the number of the ring atom from which the hydrogen is removed, if there is more than one possibility. The carboaryl groups derived from, for example, naphthalene (C_{10}) can be either napth-1-yl or nath-2-yl; and from azulene (C_{10}) can be azul-1-yl, azul-2-yl, azul-4-yl, azul-5-yl and azul-6-yl. The heteroaryl groups derived, for example, from isoquinoline can be isoquinol-x-yl (x-isoquinolyl), where x can be 1, 3, 4, 5, 6, 7 or 8.

Bi-C_{5-7} aryl: The term "Bi-C_{5-7} aryl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound with two aromatic rings, where each ring has from 5 to 7 ring atoms, and the rings are linked by a single bond.

If the ring atoms of an aromatic ring are all carbon atoms, as in a "carboaryl ring", then that ring will be derived from benzene.

One or more of the ring atoms may be a heteroatom, as in a "heteroaryl ring". Examples of heteroaryl rings include, but are not limited to:

N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);

O_1: furan (oxole) (C_5);

S_1: thiophene (thiole) (C_5);

N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);

N_2O_1: oxadiazole (furazan) (C_5);

N_3O_1: oxatriazole (C_5);

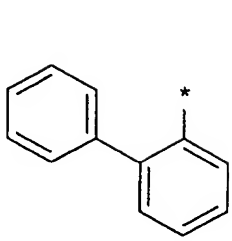
N_1S_1: thiazole (C_5), isothiazole (C_5);

N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);

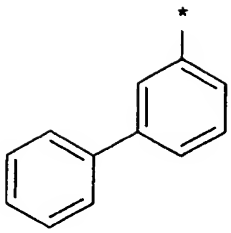
N_3: triazole (C_5), triazine (C_6); and,

N_4: tetrazole (C_5).

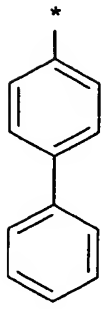
The bi-C_{5-7} aryl group includes the radical formed by removal of a hydrogen atom from any of the possible aromatic ring atoms of the 'first' aromatic ring, i.e. the ring from which the hydrogen atom is removed, and the 'second' aromatic ring, i.e. the ring from which the hydrogen atom is not removed, may be bonded to the first aromatic ring at any position in relation to the ring atom from which the hydrogen atom has been removed. For example, if both aromatic rings are unsubstituted benzene rings, then the following groups are possible:



biphen-2-yl



biphen-3-yl



biphen-4-yl

The phrase "optionally substituted", as used herein, pertains to a parent group, as above, which may be unsubstituted or which may be substituted by one of the following substituent groups:

C_{1-20} alkyl group: The term "C_{1-20} alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl and cycloalkyl discussed below.

In this context, the prefixes (e.g. C_{1-4}, C_{1-7}, C_{1-20}, C_{2-7}, C_{3-7}, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C_{1-4} alkyl," as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C_{1-4} alkyl ("lower alkyl"), C_{1-7} alkyl, and C_{1-20} alkyl.

Examples of saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), butyl (C_4),

pentyl (C_5), hexyl (C_6), heptyl (C_7), octyl (C_8), nonyl (C_9), decyl (C_{10}), n-undecyl (C_{11}), dodecyl (C_{12}), tridecyl (C_{13}), tetradecyl (C_{14}), pentadecyl (C_{15}), and eicodecyl (C_{20}).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5), n-hexyl (C_6), and n-heptyl (C_7).

Examples of saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neo-pentyl (C_5).

Cycloalkyl: The term "cycloalkyl", as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 3 to 7 ring atoms.

Examples of saturated cycloalkyl groups include, but are not limited to, those derived from: cyclopropane (C_3), cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6), cycloheptane (C_7), norbornane (C_7), norpinane (C_7), norcarane (C_7), adamantane (C_{10}), and decalin (decahydronaphthalene) (C_{10}).

Examples of saturated cycloalkyl groups, which are also referred to herein as "alkyl-cycloalkyl" groups, include, but are not limited to, methylcyclopropyl, dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl,

and dimethylcyclohexyl, menthane, thujane, carane, pinane, bornane, norcarane, and camphene.

Examples of unsaturated cyclic alkenyl groups, which are also referred to herein as "alkyl-cycloalkenyl" groups, include, but are not limited to, methylcyclopropenyl, dimethylcyclopropenyl, methylcyclobutenyl, dimethylcyclobutenyl, methylcyclopentenyl, dimethylcyclopentenyl, methylcyclohexenyl, and dimethylcyclohexenyl.

Examples of cycloalkyl groups, with one or more other rings fused to the parent cycloalkyl group, include, but are not limited to, those derived from: indene (C_9), indan (e.g., 2,3-dihydro-1H-indene) (C_9), tetraline (1,2,3,4-tetrahydronaphthalene (C_{10}), acenaphthene (C_{12}), fluorene (C_{13}), phenalene (C_{13}), acephenanthrene (C_{15}), aceanthrene (C_{16}). For example, 2H-inden-2-yl is a C_5cycloalkyl group with a substituent (phenyl) fused thereto.

Alkenyl: The term "alkenyl," as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds. Examples of groups of alkenyl groups include C_{2-4} alkenyl, C_{2-7} alkenyl, C_{2-20} alkenyl.

Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl, $-CH=CH_2$), 1-propenyl ($-CH=CH-CH_3$), 2-propenyl (allyl, $-CH-CH=CH_2$), isopropenyl ($-C(CH_3)=CH_2$), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

Examples of cyclic alkenyl groups, which are also referred to herein as "cycloalkenyl" groups, include, but are not

limited to, cyclopropenyl (C_3), cyclobutenyl (C_4), cyclopentenyl (C_5), and cyclohexenyl (C_6).

Alkynyl: The term "alkynyl," as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C_{2-4} alkynyl, C_{2-7} alkynyl, C_{2-20} alkynyl.

Examples of alkynyl groups include, but are not limited to, ethynyl (ethinyl, -C≡CH) and 2-propynyl (propargyl, -CH_2-C≡CH).

C_{3-20} heterocyclyl group: The term "C_{3-20} heterocyclyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g. C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6} heterocyclyl," as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C_{3-20} heterocyclyl, C_{3-7} heterocyclyl, C_{5-7} heterocyclyl.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:
N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole

(isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);
O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);
S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);
O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);
O_3: trioxane (C_6);
N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);
N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);
N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);
N_2O_1: oxadiazine (C_6);
O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and,
$N_1O_1S_1$: oxathiazine (C_6).

C_{5-20} Aryl: The term "C_{5-20} aryl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 5 to 7 ring atoms. The term "C_{5-7} aryl" is a subset of the term "C_{5-20} aryl" and refers to monovalent moieties obtained by removing a hydrogen atom from an aromatic compound which has from 5 to 7 ring atoms.

The ring atoms may be all carbon atoms, as in "carboaryl groups." Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C_6), naphthalene (C_{10}), azulene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}).

Alternatively, the ring atoms may include one or more heteroatoms, as in "heteroaryl groups." Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);

O_1: furan (oxole) (C_5);

S_1: thiophene (thiole) (C_5);

N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);

N_2O_1: oxadiazole (furazan) (C_5);

N_3O_1: oxatriazole (C_5);

N_1S_1: thiazole (C_5), isothiazole (C_5);

N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);

N_3: triazole (C_5), triazine (C_6); and,

N_4: tetrazole (C_5).

Examples of heteroaryl groups which comprise fused rings, include, but are not limited to:

C_9 heteroaryl groups (with 2 fused rings) derived from benzofuran (O_1), isobenzofuran (O_1), indole (N_1), isoindole (N_1), indolizine (N_1), indoline (N_1), isoindoline (N_1), purine (N_4) (e.g., adenine, guanine), benzimidazole (N_2), indazole (N_2), benzoxazole (N_1O_1), benzisoxazole (N_1O_1), benzodioxole (O_2), benzofurazan (N_2O_1), benzotriazole (N_3),

benzothiofuran (S_1), benzothiazole (N_1S_1), benzothiadiazole (N_2S);

C_{10} heteroaryl groups (with 2 fused rings) derived from chromene (O_1), isochromene (O_1), chroman (O_1), isochroman (O_1), benzodioxan (O_2), quinoline (N_1), isoquinoline (N_1), quinolizine (N_1), benzoxazine (N_1O_1), benzodiazine (N_2), pyridopyridine (N_2), quinoxaline (N_2), quinazoline (N_2), cinnoline (N_2), phthalazine (N_2), naphthyridine (N_2), pteridine (N_4);

C_{11} heteroaryl groups (with 2 fused rings) derived from benzodiazepine (N_2);

C_{13} heteroaryl groups (with 3 fused rings) derived from carbazole (N_1), dibenzofuran (O_1), dibenzothiophene (S_1), carboline (N_2), perimidine (N_2), pyridoindole (N_2); and,

C_{14} heteroaryl groups (with 3 fused rings) derived from acridine (N_1), xanthene (O_1), thioxanthene (S_1), oxanthrene (O_2), phenoxathiin (O_1S_1), phenazine (N_2), phenoxazine (N_1O_1), phenothiazine (N_1S_1), thianthrene (S_2), phenanthridine (N_1), phenanthroline (N_2), phenazine (N_2).

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C_{1-7}alkyl group (also referred to as a C_{1-7}alkoxy group, discussed below), a C_{3-20}heterocyclyl group (also referred to as a C_{3-20}heterocyclyloxy group), or a C_{5-20}aryl group (also referred to as a C_{5-20}aryloxy group), preferably a C_{1-7}alkyl group.

C_{1-7}alkoxy: -OR, wherein R is a C_{1-7}alkyl group. Examples of C_{1-7}alkoxy groups include, but are not limited to, -OMe

(methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy), -O(iBu) (isobutoxy), and -O(tBu) (tert-butoxy).

Oxo (keto, -one): =O.

Thione (thioketone): =S.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of imino groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylacyl or C_{1-7}alkanoyl), a C_{3-20}heterocyclyl group (also referred to as C_{3-20}heterocyclylacyl), or a C_{5-20}aryl group (also referred to as C_{5-20}arylacyl), preferably a C_{1-7}alkyl group. Examples of acyl groups include, but are not limited to, -C(=O)CH_3 (acetyl), -C(=O)CH_2CH_3 (propionyl), -C(=O)$C(CH_3)_3$ (t-butyryl), and -C(=O)Ph (benzoyl, phenone).

Carboxy (carboxylic acid): -C(=O)OH.

Thiocarboxy (thiocarboxylic acid): -C(=S)SH.

Thiolocarboxy (thiolocarboxylic acid): -C(=O)SH.

Thionocarboxy (thionocarboxylic acid): -C(=S)OH.

Imidic acid: -C(=NH)OH.

Hydroxamic acid: -C(=NOH)OH.

Ester (carboxylate, carboxylic acid ester, oxycarbonyl): -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh.

Acyloxy (reverse ester): -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, -OC(=O)Ph, and $-OC(=O)CH_2Ph$.

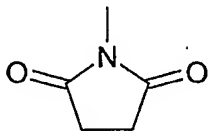
Oxycarbonyloxy: -OC(=O)OR, wherein R is an ester substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of ester groups include, but are not limited to, $-OC(=O)OCH_3$, $-OC(=O)OCH_2CH_3$, $-OC(=O)OC(CH_3)_3$, and -OC(=O)OPh.

Carbamate: $-OC(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of carbamate groups include, but are not limited to, $-OC(=O)NH_2$, $-OC(=O)NHCH_3$, $-OC(=O)N(CH_3)_2$, $-OC(=O)NHCH_2CH_3$, and $-OC(=O)N(CH_2CH_3)_2$.

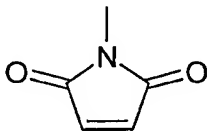
Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-C(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino

substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHCH_2CH_3$, and $-C(=O)N(CH_2CH_3)_2$, as well as amido groups in which R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

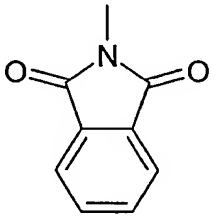
Acylamido (acylamino): $-NR^1C(=O)R^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of acylamide groups include, but are not limited to, $-NHC(=O)CH_3$, $-NHC(=O)CH_2CH_3$, and $-NHC(=O)Ph$. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



succinimidyl



maleimidyl



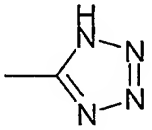
phthalimidyl

Thioamido (thiocarbamyl): $-C(=S)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of thioamido groups include, but are not limited to, $-C(=S)NH_2$, $-C(=S)NHCH_3$, $-C(=S)N(CH_3)_2$, and $-C(=S)NHCH_2CH_3$.

Ureido: $-N(R^1)CONR^2R^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R^1 is a ureido substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of ureido groups include, but are not limited to, $-NHCONH_2$, -NHCONHMe, -NHCONHEt, $-NHCONMe_2$, $-NHCONEt_2$, -NMeCONH$_2$, -NMeCONHMe, -NMeCONHEt, $-NMeCONMe_2$, and $-NMeCONEt_2$.

Guanidino: $-NH-C(=NH)NH_2$.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylamino or di-C_{1-7}alkylamino), a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary ($-NH_2$), secondary ($-NHR^1$), or tertiary ($-NHR^1R^2$), and in cationic form, may be quaternary ($-^+NR^1R^2R^3$). Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHC(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and -NHPh. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

Amidine (amidino): -C(=NR)NR_2, wherein each R is an amidine substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group. Examples of amidine groups include, but are not limited to, -C(=NH)NH_2, -C(=NH)NMe_2, and -C(=NMe)NMe_2.

Nitro: -NO_2.

Nitroso: -NO.

Cyano (nitrile, carbonitrile): -CN.

Sulfhydryl (thiol, mercapto): -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C_{1-7}alkyl group (also referred to as a C_{1-7}alkylthio group), a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of C_{1-7}alkylthio groups include, but are not limited to, -SCH_3 and -SCH_2CH_3.

Disulfide: -SS-R, wherein R is a disulfide substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group (also referred to herein as C_{1-7}alkyl disulfide). Examples of C_{1-7}alkyl disulfide groups include, but are not limited to, -$SSCH_3$ and -$SSCH_2CH_3$.

Sulfine (sulfinyl, sulfoxide): -S(=O)R, wherein R is a sulfine substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a

C_{1-7}alkyl group. Examples of sulfine groups include, but are not limited to, $-S(=O)CH_3$ and $-S(=O)CH_2CH_3$.

Sulfone (sulfonyl): $-S(=O)_2R$, wherein R is a sulfone substituent, for example, a C_{1-7}alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7} alkyl group, including, for example, a fluorinated or perfluorinated C_{1-7}alkyl group. Examples of sulfone groups include, but are not limited to, $-S(=O)_2CH_3$ (methanesulfonyl, mesyl), $-S(=O)_2CF_3$ (triflyl), $-S(=O)_2CH_2CH_3$ (esyl), $-S(=O)_2C_4F_9$ (nonaflyl), $-S(=O)_2CH_2CF_3$ (tresyl), $-S(=O)_2CH_2CH_2NH_2$ (tauryl), $-S(=O)_2Ph$ (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

Sulfinic acid (sulfino): $-S(=O)OH$, $-SO_2H$.

Sulfonic acid (sulfo): $-S(=O)_2OH$, $-SO_3H$.

Sulfinate (sulfinic acid ester): $-S(=O)OR$; wherein R is a sulfinate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinate groups include, but are not limited to, $-S(=O)OCH_3$ (methoxysulfinyl; methyl sulfinate) and $-S(=O)OCH_2CH_3$ (ethoxysulfinyl; ethyl sulfinate).

Sulfonate (sulfonic acid ester): $-S(=O)_2OR$, wherein R is a sulfonate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonate groups include, but

are not limited to, $-S(=O)_2OCH_3$ (methoxysulfonyl; methyl sulfonate) and $-S(=O)_2OCH_2CH_3$ (ethoxysulfonyl; ethyl sulfonate).

Sulfinyloxy: $-OS(=O)R$, wherein R is a sulfinyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-OS(=O)CH_3$ and $-OS(=O)CH_2CH_3$.

Sulfonyloxy: $-OS(=O)_2R$, wherein R is a sulfonyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonyloxy groups include, but are not limited to, $-OS(=O)_2CH_3$ (mesylate) and $-OS(=O)_2CH_2CH_3$ (esylate).

Sulfate: $-OS(=O)_2OR$; wherein R is a sulfate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfate groups include, but are not limited to, $-OS(=O)_2OCH_3$ and $-SO(=O)_2OCH_2CH_3$.

Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide): $-S(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-S(=O)NH_2$, $-S(=O)NH(CH_3)$, $-S(=O)N(CH_3)_2$, $-S(=O)NH(CH_2CH_3)$, $-S(=O)N(CH_2CH_3)_2$, and $-S(=O)NHPh$.

Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide): $-S(=O)_2NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of

sulfonamido groups include, but are not limited to, $-S(=O)_2NH_2$, $-S(=O)_2NH(CH_3)$, $-S(=O)_2N(CH_3)_2$, $-S(=O)_2NH(CH_2CH_3)$, $-S(=O)_2N(CH_2CH_3)_2$, and $-S(=O)_2NHPh$.

Sulfamino: $-NR^1S(=O)_2OH$, wherein R^1 is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to, $-NHS(=O)_2OH$ and $-N(CH_3)S(=O)_2OH$.

Sulfonamino: $-NR^1S(=O)_2R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonamino groups include, but are not limited to, $-NHS(=O)_2CH_3$ and $-N(CH_3)S(=O)_2C_6H_5$.

Sulfinamino: $-NR^1S(=O)R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinamino groups include, but are not limited to, $-NHS(=O)CH_3$ and $-N(CH_3)S(=O)C_6H_5$.

The above listed substituent groups, may themselves be further substituted, where appropriate, by one or more of themselves.

Includes Other Forms

Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional

protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

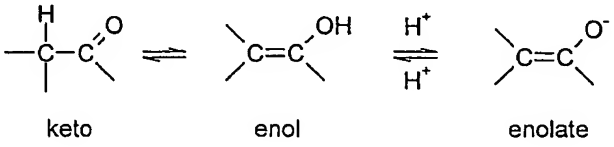
Isomers, Salts, Solvates and Protected Forms

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

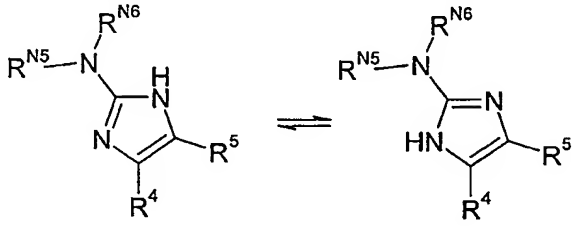
Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include

structurally isomeric forms falling within that class (e.g., C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hyroxyazo, and nitro/aci-nitro.



Tautomeric forms of particular relevance to the present invention include those of formula II, as illustrated below:



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly

or partially) racemic and other mixtures thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino

acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A wide variety of such "protecting", "blocking", or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other

functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>$C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulfonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O·).

For example, a carboxylic acid group may be protected as an ester for example, as: an C_{1-7}alkyl ester (e.g., a methyl

ester; a t-butyl ester); a C_{1-7}haloalkyl ester (e.g., a C_{1-7}trihaloalkyl ester); a triC_{1-7}alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20}aryl-C_{1-7}alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether ($-S-CH_2NHC(=O)CH_3$).

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included.

The term "therapeutically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen. Suitable dose ranges will typically be in the range of from 0.01 to 20 mg/kg/day, preferably from 0.1 to 10 mg/kg/day.

Compositions and their administration

Compositions may be formulated for any suitable route and

means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

For solid compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like may be used. The active compound as defined above may be formulated as suppositories using, for example, polyalkylene glycols, acetylated triglycerides and the like, as the carrier. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc, an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and

the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s) in an amount effective to alleviate the symptoms of the subject being treated.

Dosage forms or compositions containing active ingredient in the range of 0.25 to 95% with the balance made up from non-toxic carrier may be prepared.

For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, cellulose, cellulose derivatives, sodium crosscarmellose, starch, magnesium stearate, sodium saccharin, talcum, glucose, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain 1%-95% active ingredient, more preferably 2-50%, most preferably 5-8%.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to

injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, triethanolamine sodium acetate, etc.

The percentage of active compound contained in such parental compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.1% to 10% in solution are employable, and will be higher if the composition is a solid which will be subsequently diluted to the above percentages. Preferably, the composition will comprise 0.2-2% of the active agent in solution.

Acronyms

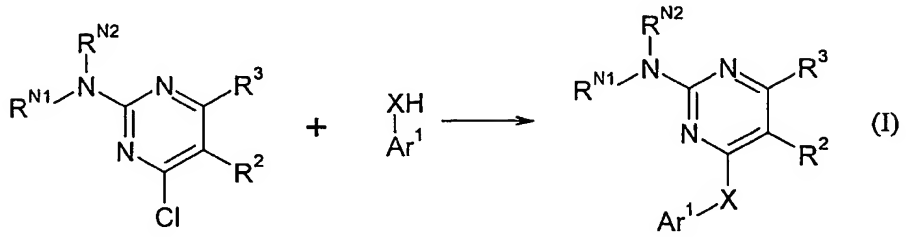
For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et_2O), acetic acid (AcOH), dichloromethane (methylene chloride,

DCM), acetonitrile (ACN), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

General Synthesis Methods

Compounds of formula I can be synthesised by the following route:



Route 1

wherein R^2, R^3, R^{N1} and R^{N2} are as defined above, and Ar^1 is either R^1, as defined above (i.e. an optionally substituted C_{9-14} aryl group or an optionally substituted C_{5-7} aryl group, which includes an optionally substituted bi-C_{5-7} aryl group) or the first aromatic ring of the bi-C_{5-7} aryl group with a moiety for attaching the second aromatic ring of the bi-C_{5-7} aryl group. In the latter case, the method of route 1 is followed by a further step of joining the second aromatic ring of the bi-C_{5-7} aryl group to the first aromatic ring.

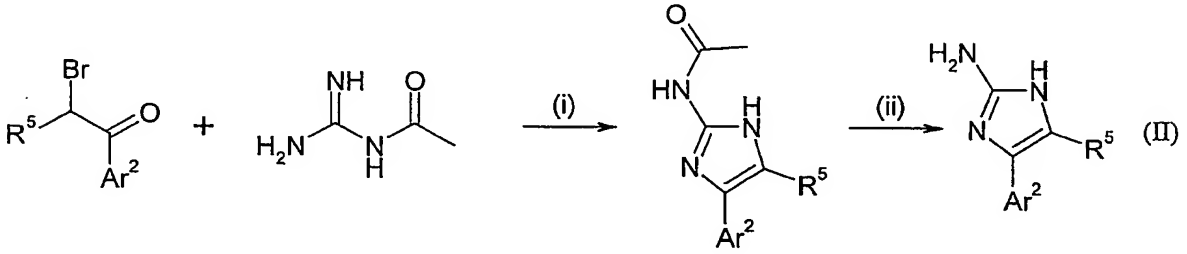
The method of route 1 is carried out in solution (for example, aqueous) optionally in the presence of base with heating (for example, microwave heating).

If Ar^1 is only the first aromatic ring of the bi-C_{5-7} aryl group, then it preferably bears either:
(i) a halogen, such as bromo, iodo or chloro, or a group which is subsequently converted into a triflic group, for example a protected alcohol; or

(ii) a group, such as bromo or iodo, which is subsequently converted into, for example, a boronic acid group or derivative thereof, or certain magnesium, tin or zinc containing organometallic reagents.

The second aromatic ring of the bi-C_{5-7} aryl group bears the other of the final groups of (i) and (ii) above, such that the two rings may be joined by a palladium catalysed coupling reaction. The palladium catalyst may be tetrakis(triphenylphosphine)palladium(0), and the reaction may be carried out in the presence of an inorganic base, such as sodium carbonate. The reaction is usually carried out by heating at about 80-90°C for several hours.

Compounds of formula II, where R^{N5} and R^{N6} are H, can be synthesised by the following route:



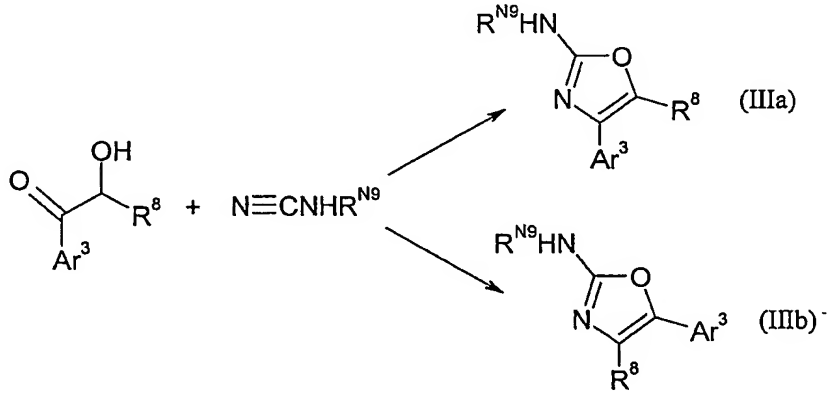
Route 2

wherein R^5 is as defined above, and Ar^2 is either R^4, as defined above (i.e. an optionally substituted C_{9-14} aryl group or an optionally substituted bi-C_{5-7} aryl group) or the first aromatic ring of the bi-C_{5-7} aryl group with a moiety for attaching the second aromatic ring of the bi-C_{5-7} aryl group. In the latter case, the method of route 2 includes a further step of joining the second aromatic ring of the bi-C_{5-7} aryl group to the first aromatic ring. This further step may occur between steps (i) and (ii), or after step (ii).

Step (i) is usually carried out by heating the two reactants in organic solvent (for example, DMF). The second step, which is the removal of the acetyl group is carried out under standard conditions, for example, in a 5:1 mixture of industrial methylated spirits and water in the presence of concentrated sulfuric acid, followed by basification.

If Ar^2 is only the first aromatic ring of the bi-C_{5-7} aryl group, then its preferred substituents and method of joing the second aromatic ring are as above for Ar^1.

Compounds of formula IIIa and IIIb where at least one of R^{N9} and R^{N10} is hydrogen can be synthesised following the route disclosed by Cockerill (Cockerill, A.F., *et al.*, *Synthesis*, 1976, 591-593 which is incorporated herein by reference).



Route 3

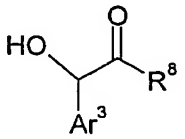
where R^8 and R^{N9} are as defined), and Ar^3 is either R^7, as defined above (i.e. an optionally substituted bi-C_{5-7} aryl group) or the first aromatic ring of the bi-C_{5-7} aryl group with a moiety for attaching the second aromatic ring of the bi-C_{5-7} aryl group. In the latter case, the method of route 3 includes a further step of joining the second aromatic ring of the bi-C_{5-7} aryl group to the first aromatic ring.

In this method the 2-amino oxazole is produced by the condensation of the appropriate α-hydroxy ketone with cyanamide or alkylcyanamide, which reaction can be carried out in aqueous solution or in the presence of a mineral acid or a base catalyst (e.g. sodium hydroxide).

The inventors have found that product of the reaction may be either the 2-amino-4-aryl oxazole, the 2-amino-5-aryl oxazole, or a mixture of the two, with the 2-amino-5-aryl oxazole being favoured. It is thought that carrying the reaction out under milder conditions may increase the amount of the 2-amino-4-aryl oxazole produced.

If the product of the method is a mixture of compounds of formula IIIa and IIIb these may be separated by column chromatography.

Without wishing to be bound by theory, the product of formula IIIb results from the reaction of the tautomeric form of the starting material:



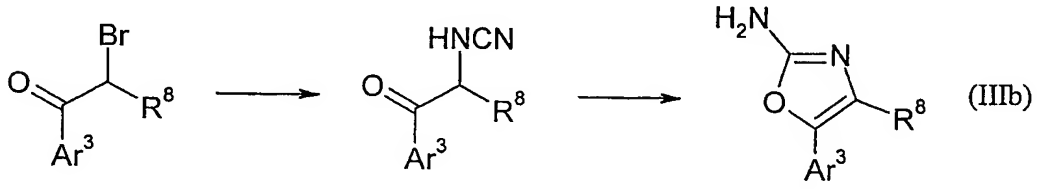
The two tautometric forms of the starting material exist in equilibrium, which under the conditions of the reaction tends to favour the formation of IIIb rather than IIIa.

The starting α-hydroxyketones can be synthesised via α-bromo and α-acetoxy intermediates, some of which are commercially available, from the parent ketones.

The substitution on the 2-amino group can be introduced using a substituent on the cyanamide, or may be introduced

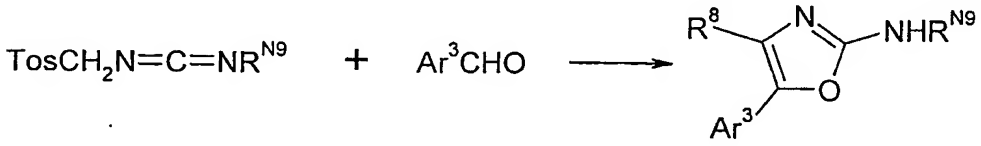
later in the reaction scheme, again with, if necessary, protection of other functional groups in the molecule.

The compounds of formula IIIb when R^{N9} and R^{N10} represent hydrogen may also be obtained regio-specifically be reacting an α-bromoketone with cyanamide in ethanol in the presence of sodium ethoxide and proceeds via a cyano α-aminoketone, as shown in Route 4:



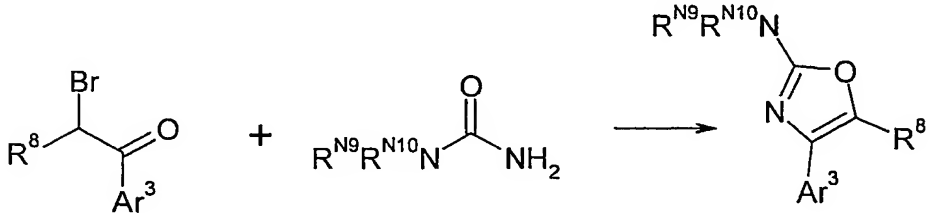
Route 4

Compounds of formula IIIb where R^8 is hydrogen and R^{N9} and R^{N10} are hydrogen or an alkyl group may also be preared by a stereoselective method described by van Leusen, *et al.*, *J. Org. Chem.*, 46, 2069-2072(1981), which is incorporated herein by reference, that employs the reaction of an N-tosylmethylcarbodiimide with an aromatic aldehyde in a solvent, such as methylene chloride, in the presence of a base (e.g. aqueous sodium hydroxide) and a phase transfer catalyst (e.g. tetrabutylammonium bromide), as shown in Route 5. For compounds where R^{N9} is hydrogen, the group R^{N9} in the carbodiimide is a trityl group that is removed after condensing with the aldehyde by treatment with mineral acid.



Route 5

Compounds of formula IIIa can be prepared by following the route (Route 6) described by Gompper, R., and Christmann, O., *Chem. Ber.* 92, 1944 -1949 (1959), which is incorporated herein by reference, in which the 2-amino or 2-alkylamino oxazole is produced by condensing the appropriate α-bromo ketone with urea or substituted urea, which reaction is carried out in an organic solvent, e.g. dimethylformamide.



Route 6

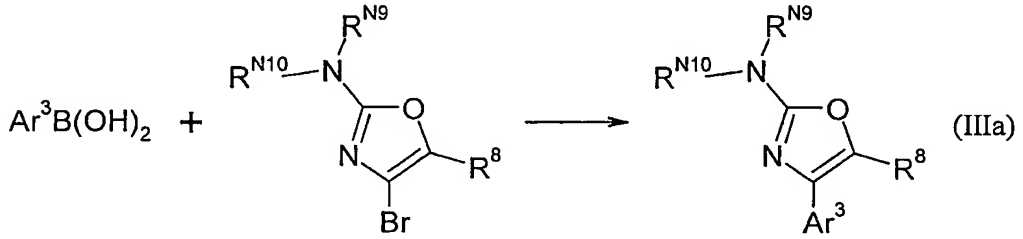
The 5-substituent on the oxazole ring is present in the starting material as the alkyl chain of the α-bromo alkylarylketone, which can be obtained from the parent alkylarylketone if necessary.

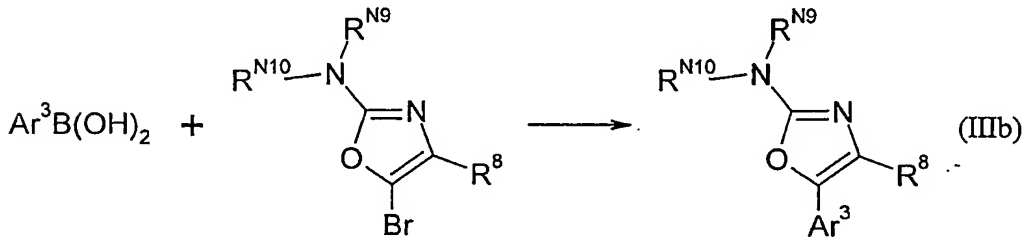
This route can be used for compounds of formula IIIa where R^7 is an optionally substituted C_{9-14} aryl group and R^{N9} and R^{N10} are hydrogen or alkyl groups but is less preferred for these compounds.

The starting ketones for both routes are either commercially available or accessible by, for example, Grignard reactions on the corresponding nitriles or Friedal Crafts reaction of substituted aryls.

A further method of preparing compounds of formula IIIa and IIIb respectively is by a palladium catalysed coupling reaction of a 2-amino-4-substituted oxazole or 2-amino-5-substituted oxazole with an aryl boronic acid, or derivative thereof. The 4- or 5-substituent on the oxazole ring may

typically be a halogen, such as bromo, iodo or chloro, or a group such as trifluoromethanesulfonate or a phophate ester. The aryl boronic acid may also be replaced by certain magnesium, tin or zinc containing organometallic reagents. For example, a 2-amino-4-bromo-oxazole may be reacted with an aryl boronic acid derivative in an aqueous solvent, for example a mixture of ethanol, water and dimethoxyethane, containing a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) and an inorganic base such as sodium carbonate. The reaction is carried out by heating at about 80-90°C for several hours.





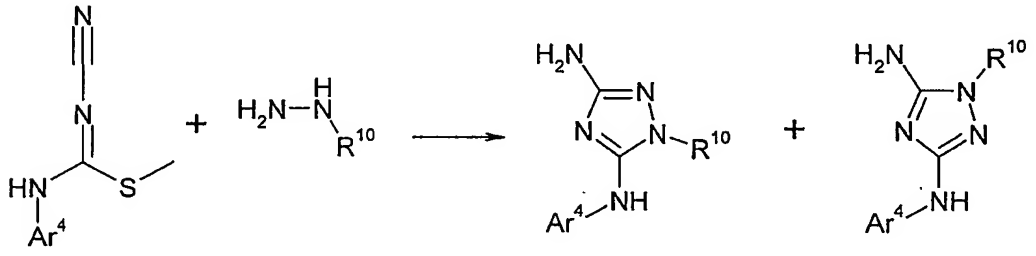
Route 7

Alternatively, the boronic acid residue, or equivalent, may be on the 4-position of the oxazole ring and the halogen, or equivalent, on the aryl group.

If Ar^3 in the above route represents only the first aromatic ring of the bi-C_{5-7} aryl group, then appropriate protection, or the use of precursor groups, may be required to prevent unwanted side reactions.

Compounds of formulae IIIa and IIIb may also be prepared by nucleophilic displacement of the intermediate chloro compounds with ammonia or amines as described, for example, by Marchetti, E., *et al.*, *J. Med. Chem.*, **11**, 1092-1093 (1968), which are incorporated herein by reference.

Compounds of formulae IVa and IVb, where R^{N13} and R^{N14} are both hydrogen, may be synthesised by the following route following that described in Reiter, J. and Pongo, L., *J. Het. Chem.*, **23**, 401-408 (1986), which is incorporated herein by reference:



(IVa) (IVb)

Route 8

where Ar^4 is either R^7, as defined above (i.e. an optionally substituted C_{9-14} aryl group or an optionally substituted bi-C_{5-7} aryl group) or the first aromatic ring of the bi-C_{5-7} aryl group with a moiety for attaching the second aromatic ring of the bi-C_{5-7} aryl group. In the latter case, the method of route 2 includes a further step of joining the second aromatic ring of the bi-C_{5-7} aryl group to the first aromatic ring.

If the reaction does result in a mixture of a compound of formula IVa and a compound of formula IVb, then these may be separated using, for example, column chromatography.

In any of the above routes, any substitution on the C_{9-14} aryl group or bi-C_{5-7} aryl group is preferably present in the relevant starting material, but could be introduced later in the reaction scheme, with, if necessary, appropriate protection of other functional groups present in the molecule. Derivation of the amino group attached to the central ring of the compound is possible to provide varied groups at that position.

Preferences

The following preferences may be combined with one another, and may be different for each aspect of the present invention.

The optional substituents for all groups are preferably independently selected from halo, hydroxy, alkoxy (more preferably C_{1-4} alkoxy), amino (more preferably NH_2, C_{1-4} alkyl amino, C_{1-4} dialkyl amino), and amido (more preferably $CONH_2$, C_{1-4} alkyl amido, C_{1-4} dialkyl amido)

Pyrimidines

R^{N1} and R^{N2}

In some embodiments it is preferred that both R^{N1} and R^{N2} are substituted, and in other embodiments that only one or neither of R^{N1} and R^{N2} are substituted. Each of R^{N1} and R^{N2} are preferably independently selected from H, R, R', where R and R' are as defined above, and more preferably selected from H and R. R is preferably an optionally substituted C_{1-4} alkyl group. The preferred substituents for R and R' include halo, hydroxy, amino and acetyl. R^{N1} and R^{N2} are more preferably independently selected from H and methyl, and are most preferably both H.

R^2

R^2 is preferably selected from H, optionally substituted C_{1-6} alkyl and optionally substituted C_{3-7} cycloalkyl, more preferably from H and unsubstituted C_{1-6} alkyl (preferably methyl) and is most preferably H.

R^3

R^3 is preferably selected from H, optionally substituted C_{1-6} alkyl and optionally substituted C_{3-7} cycloalkyl(especially when X is NH), more preferably from H and optionally substituted C_{1-6} alkyl (preferably methyl and ethyl) and is most preferably methyl.

X

X is preferably NH.

R^1

R^1 is preferably an optionally substituted C_{9-14} aryl group (more preferably naphthyl) or an optionally substituted bi-C_{5-7} aryl group (more preferably bi-C_6 aryl, most preferably bi-phenyl). This preference for R^1 is especially preferred when R^{N1}, R^{N2} and R^2 are H, R^3 is methyl and X is NH.

If R^1 is an optionally substituted C_{5-7} aryl group (preferably phenyl), then it preferably bears an halo group at the meta position, and may be further substituted, in particular with halo groups.

If R^1 is an optionally substituted C_{5-7} aryl group, then it is preferred that is is not substituted by a carbonyl based group, for example amido. It is also preferred that the sole substituent is not in the ortho position.

If X is O, then it is preferred that R^1 is a C_{9-14} aryl group or a bi-C_{5-7} aryl group, where the second aryl group is meta to the first.

If R^1 is an optionally substituted bi-C_{5-7} aryl group, then preferred substituents include, but are not limited to, C_{1-4} alkyl (preferably methyl), hydroxy, C_{1-4} alkoxy (preferably methoxy) and NH_2. It is preferred that the substituent is not acylamido or a sulfur based group (e.g. sulfonyl).

If R^1 is an optionally substituted bi-C_{5-7} aryl group, then it is preferably a bi-C_6 aryl group and is more preferably a bi-phenyl group. Most preferably R^1 is a 3-phenyl-phenyl group. It is preferred that any subtituent is on the distal phenyl ring, preferably at the 2-position.

If R^1 is an optionally substituted C_{9-14} aryl group, preferred substituent groups for the C_{9-14} aryl group (especially when X is O) include halo, hydroxy, C_{1-4} alkoxy, cyano, amino, amido and C_{1-4} alkyl, of which hydroxy, and C_{1-4} alkoxy are more preferred. It is also preferred that the C_{9-14} aryl group bears no oxo substituents.

If the C_{9-14} aryl group is a naphth-1-yl group, preferred substituent positions are 2, 4 and 7, with 2 being most preferred. The preferred substituents at the 2-position are hydroxy, C_{1-4} alkyl and C_{1-4} alkoxy, with C_{1-4} alkoxy (e.g. methoxy and ethoxy) being most preferred.

Imidazoles

R^{N5} and R^{N6}

In some embodiments it is preferred that both R^{N5} and R^{N6} are

substituted, and in other embodiments that only one or neither of R^{N5} and R^{N6} are substituted. Each of R^{N5} and R^{N6} are preferably independently selected from H, R, R' and C(=O)R, where R and R' are as defined above, and more preferably selected from H, R and C(=O)R. R is preferably an optionally substituted C_{1-4} alkyl group. The preferred substituents for R and R' include halo, hydroxy, amino and acetyl. More preferably, at least one of R^{N5} and R^{N6} is H, and the other is selected from H and C(=O)Me. There is a preference for at least one of R^{N5} and R^{N6} to be R, R', SO_2R, C(=O)R, $(CH_2)_nNR^{N7}R^{N8}$, when R^4 is an unsubstituted 4-phenyl-phenyl group.

R^5

R^5 is preferably selected from H, optionally substituted C_{1-6} alkyl and optionally substituted C_{3-7} cycloalkyl, more preferably from H and unsubstituted C_{1-6} alkyl (preferably methyl, and $-C(CH_3)_2$) and is most preferably H. There is a preference for R^5 to be an optionally substituted C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl and phenyl-C_{1-4} alkyl, with a further preference for C_{1-6} alkyl, especially C_{1-3} alkyl (e.g. methyl, iso-propyl), when R^4 is an unsubstituted naphthyl group.

R^4

R^4 is preferably an optionally substituted C_{9-14} aryl group or an optionally substituted 3- or 4-C_{5-6}aryl-C_{5-6} aryl group (for example, 3-phenyl-phenyl and 4-phenyl-phenyl).

R^4 is preferably optionally substituted C_{9-14} carboaryl group, for example, naphth-1-yl, naphth-2-yl, anthracen-1-yl, anthracen-2-yl, anthracen-9-yl, phenanthren-1-yl, phenanthren-2-yl, phenanthren-3-yl and phenanthren-4-yl,

phenanthren-9-yl. Of these napth-1-yl and napth-2-yl are preferred, with naphthy-1-yl being most preferred. Other preferred R^4 groups include benzo[b]thiophen-2-yl, benzo[b]thiophen-4-yl and benzo[1,4]dioxin-5-yl.

Preferred substituent groups for the C_{9-14} aryl group include halo, hydroxy, C_{1-4} alkoxy, cyano, amino, amido and C_{1-4} alkyl, of which hydroxy, fluoro and C_{1-4} alkoxy are more preferred. It is also preferred that the C_{9-14} aryl group bears no oxo substituents.

If the C_{9-14} aryl group is a naphth-1-yl group, preferred substituent positions are 2, 4 and 7, with 2 being most preferred. The preferred substituents at the 2-position are hydroxy, C_{1-4} alkyl and C_{1-4} alkoxy, with C_{1-4} alkoxy (e.g. methoxy and ethoxy) being most preferred.

Oxazoles

It is preferred that the compounds are of formula (IIIb).

R^8 is preferably selected from H and optionally substituted C_{1-6} alkyl and C_{3-7} cycloalkyl, more preferably H and optionally substituted C_{1-6} alkyl. Especially preferred are H, and C_{1-4} alkyl (e.g. methyl, *iso*-propyl). In some embodiments the group may be unsubstituted, but when the group is substituted, preferred substituent groups include halo, hydroxy, and amino. Most preferably, R^8 is H or methyl.

In some embodiments it is preferred that both R^{N9} and R^{N10} are substituted, and in other embodiments that only one or neither of R^{N9} and R^{N10} are substituted. Each of R^{N9} and R^{N10} are preferably independently selected from H, R, R', where R

and R′ are as defined above, and more preferably selected from H and R. R is preferably an optionally substituted C_{1-4} alkyl group. The preferred substituents for R and R′ include halo, hydroxy, amino and acetyl.

R^7 is preferably an optionally substituted bi-C_6 aryl group and is more preferably a bi-phenyl group. Most preferably R^7 is a 3-phenyl-phenyl group or a 2-phenyl-phenyl group. The phenyl groups are preferably either unsubstituted or substituted with an alkoxy (preferably methoxy), halo (preferably chloro), C_{1-4} alkyl (preferably methyl or iso-propyl) or hydroxy. It is preferred that the subtituent is on the distal phenyl ring, preferably at the 2-position.

Triazoles

It is preferred that the compounds are of formula (IVb).

R^{10} is preferably selected from H, and C_{1-4} alkyl (e.g. methyl, *iso*-propyl) and more preferably C_{1-4} alkyl. In some embodiments the group may be unsubstituted, but when the group is substituted, preferred substituent groups include halo, hydroxy, and amino. Most preferably, R^{10} is methyl.

In some embodiments it is preferred that both R^{N13} and R^{N14} are substituted, and in other embodiments that only one or neither of R^{N9} and R^{N10} are substituted. Each of R^{N13} and R^{N14} are preferably independently selected from H, R, R′, where R and R′ are as defined above, and more preferably selected from H and R. R is preferably an optionally substituted C_{1-4} alkyl group. The preferred substituents for R and R′ include halo, hydroxy, amino and acetyl.

R^9 is preferably an optionally substituted bi-C_6 aryl group

and is more preferably a bi-phenyl group. Most preferably R^9 is a 3-phenyl-phenyl group. The phenyl groups are preferably either unsubstituted or substituted with an alkoxy (preferably methoxy), halo (preferably chloro), C_{1-4} alkyl (preferably methyl or iso-propyl) or hydroxy. It is preferred that the subtituent is on the distal phenyl ring, preferably at the 2-position.

The selectivity of the compound for antagonising 5-HT_{2B} receptors over 5-HT_{2A} and/or 5-HT_{2C} receptors can be quantified by dividing the Ki for 5-HT_{2B} (see below) by the Ki for 5-$HT_{2A/2C}$ (see below). The resulting ratio is preferably 10 or more, more preferably 100 or more.

The following examples illustrate the invention.

Preparative HPLC System

Preparative HPLC was carried out on a C18-reverse-phase column (10 x 2.1 cm i.d Genesis column with 7 µm particle size), eluting with a gradient of acetonitrile (containing 0.1% trifluoroacetic acid) in water (containing 0.1% trifluoroacetic acid) at a flow rate of 5ml/min. UV detection at 230 nm was used unless otherwise stated.

LC/MS Systems

The Liquid Chromatography Mass Spectroscopy (LC/MS) systems used:

LC/MS System A:

Mass Spectrometer - Platform LC with electrospray source operating in positive and negative Ion mode. HP1100 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1100 DAD detection and SEDEX ELS detection.

Mobile Phase: A) Water 0.1 % Formic Acid
B) Acetonitrile 0.1% Formic Acid

Gradient

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.50	2.0	5	95
5.00	2.0	5	95
5.50	2.0	95	5

Column - Luna 3u C18(2) 30x4.6mm

LC/MS System B:
Mass Spectrometer - Finnigan TSQ700 with electrospray source operating in positive or negative ion mode. HP1050 system running at 2.0 mL/min, 200 µL/min split to the ESI source with inline HP1050 Single Wavelength UV detector at 254 nm.

Mobile Phase: A) Water 0.1 % formic Acid
B) Acetonitrile 0.1% formic Acid

Gradient:

Time (min)	Flow (mL/min)	%A	%B
0.00	2.0	95	5
1.00	2.0	95	5
15.00	2.0	5	95
17.00	2.0	5	95
18.00	2.0	95	5
20.00	2.0	95	5

Column - Higgins Clipius C18 5um 100 x 3.0mm

^{1}H NMR system

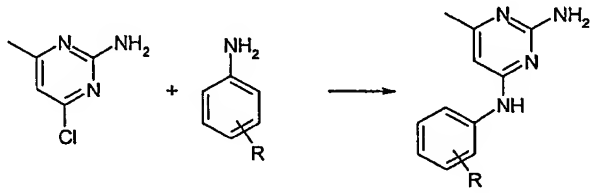
The ^{1}H NMR spectra were recorded on a Varian Unity Inova 400, which operates at 400 MHz for ^{1}H. It is equipped with a 5mm inverse detection triple resonance probe for detection of ^{1}H. The magnetic field is provided by a 9.4 Tesla Oxford instruments super-conducting magnet. The host computer is a Sun Microsystems SunBlade 1000 workstation.

Microwave system

Where microwave heating is specified, the Smith Synthesizer™ was used.

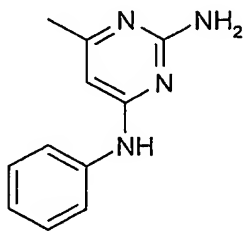
Example 1

Example 1(a)(i): Synthesis of *N*^{4}-aryl-6-methyl-pyrimidine-2,4-diamines



(1) (2)

N^4*-phenyl-6-methyl-pyrimidine-2,4-diamine hydrochloric acid (2A)*



In a microwave vial (5 mL) was placed 2-amino-4-chloro-6-methylpyrimidine (143 mg), aniline (1A, 92 μL) and water (3 mL). The vessel was sealed with a crimped septum cap, and placed in the microwave cavity. The vial was heated at 165°C for 10 minutes, after this time the vial was allowed to cool to room temperature, whereupon the title compound was purified by RP-HPLC (24 mg, 6 %) as a pale pink solid. LC/MS System B: R_t = 2.75 min, m/z (ES^+) = 201 ((M+H) for $C_{11}H_{12}N_4$).

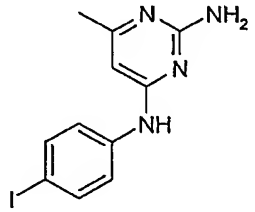
Compounds 2E-2K, 2M-2AK

Similarly, replacing aniline with other compounds of formula (1):

4-iodoaniline (Compound 1E);
4-bromoaniline (Compound 1F);
3-iodoaniline (Compound 1G);
3-(trifluoromethyl)aniline (Compound 1H);
4-fluoroaniline (Compound 1I);
5-aminoindane (Compound 1J);
4-morpholinoaniline (Compound 1K);
3,4-difluoroaniline (Compound 1M);
3,4-dichloroaniline (Compound 1N);
2-amino-4-bromophenol (Compound 1O);
3,4-dimethoxyaniline (Compound 1P);
3-aminophenol (Compound 1Q);
4-aminoindane (Compound 1R);
3-bromo-4-methylaniline (Compound 1S);
3-bromo-2-methylaniline (Compound 1T);
4-methylaniline (Compound 1U);
4'-aminoacetanilide (Compound 1V);
4-amino-benzamide (Compound 1W);
3-aminobenzylalcohol (Compound 1X);
3-chloro-4-iodoaniline (Compound 1Y);

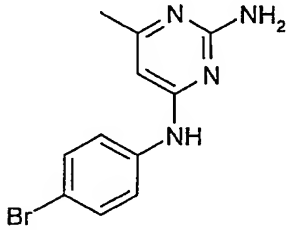
3-amino-benzamide (Compound 1Z);
6-amino-indan-1-one (Compound 1AA);
6-aminobenzothiazole (Compound 1AB);
3-chloro-4-methoxyaniline (Compound 1AC);
3-phenoxyaniline (Compound 1AD);
4-phenoxyaniline (Compound 1AE);
3-bromoaniline (Compound 1AF);
2-iodoaniline (Compound 1AG);
2-phenoxyaniline (Compound 1AH);
4-(trifluromethyl)aniline (Compound 1AI);
2,5-dibromoaniline (Compound 1AJ);
3-iodo-4-methylaniline (Compound 1AK);
and following the procedures of preparation of 2A above, the following compounds of the formula (2) were prepared:

N^4-(4-iodo-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2E):



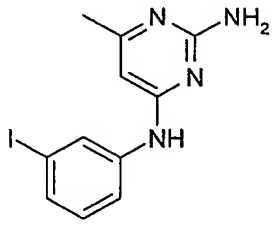
(170 mg, 47 %) as an olive coloured solid. LC/MS System B: R_t = 4.69 min, m/z (ES^+) = 327 ((M+H) for $C_{11}H_{11}IN_4$).

N^4-(4-bromo-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2F):



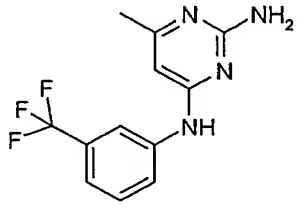
(191 mg, 61 %) as a white solid. LC/MS System B: R_t = 4.23 min, m/z (ES^+) = 279, 281 for ((M+H) for $C_{11}H_{11}BrN_4$).

N^4-(3-iodo-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2G):



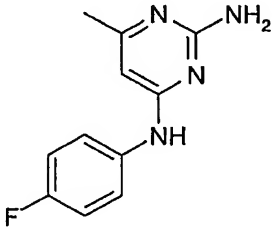
(204 mg, 56 %) as a white solid. LC/MS System B: R_t = 4.48 min, m/z (ES^+) = 327 ((M+H) for $C_{11}H_{11}IN_4$).

6-Methyl-N^4-(3-trifluoromethyl-phenyl)-pyrimidine-2,4-diamine, hydrochloride (2H):



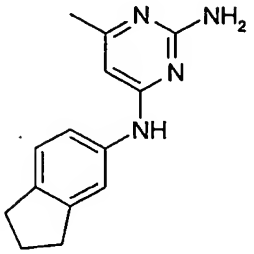
(207 mg, 68 %) as a white solid. LC/MS System B: R_t = 4.68 min, m/z (ES^+) = 269 ((M+H) for $C_{12}H_{11}F_3N_4$).

N^4-(4-fluoro-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2I):



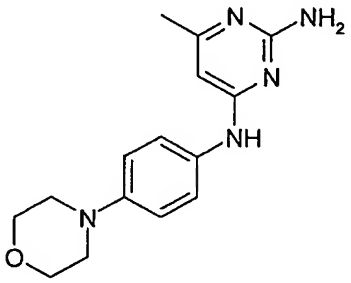
(92 mg, 36 %) as a white solid. LC/MS System B: R_t = 3.4 min, m/z (ES^+) = 219 ((M+H) for $C_{11}H_{11}FN_4$).

N^4-indan-5-yl-6-methyl-pyrimidine-2,4-diamine hydrochloride (2J):



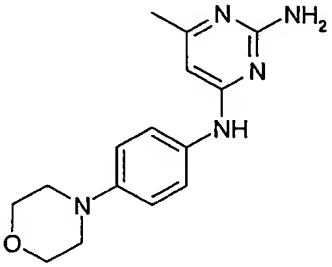
(220 mg, 79 %) as a fawn coloured solid. LC/MS System B: R_t = 4.64 min, m/z (ES^+) = 241 ((M+H) for $C_{14}H_{16}N_4$).

6-methyl-N^4-(4-morpholin-4-yl-phenyl)-pyrimidine-2,4-diamine hydrochloride (2K):



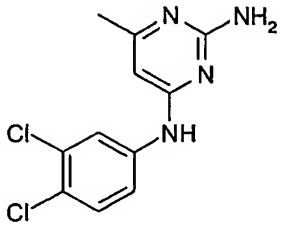
(254 mg, 79 %) as a grey coloured solid. LC/MS System B: R_t = 3.19 min, m/z (ES^+) = 286 ((M+H) for $C_{15}H_{19}N_5O$).

N^4-(3,4-difluoro-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2M):



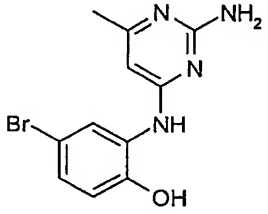
(51 mg, 19 %) as a cream coloured solid. LC/MS System B: R_t = 3.67 min, m/z (ES^+) = 237 ((M+H) for $C_{11}H_{10}F_2N_4$).

N^4-(3,4-dichloro-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2N):



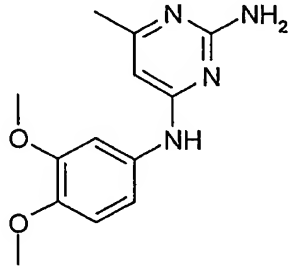
(246 mg, 80 %) as a fawn coloured solid. LC/MS System B: R_t = 4.42 min, m/z (ES^+) = 269, 271 for ((M+H) for $C_{11}H_{10}Cl_2N_4$).

2-(2-amino-6-methyl-pyrimidin-4-ylamino)-4-bromo-phenol hydrochloride (2O):



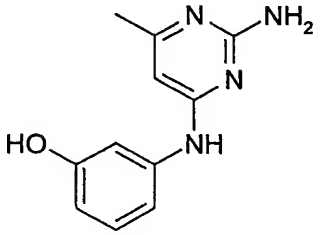
(127 mg, 38 %) as a brown coloured solid. LC/MS System B: R_t = 3.59 min, m/z (ES^+) = 295, 297 ((M+H) for $C_{11}H_{11}BrN_4O$).

N^4-(3,4-dimethoxy-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2P):



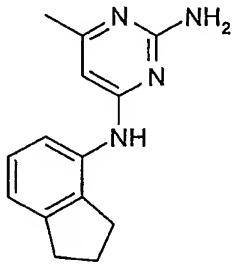
(66 mg, 22 %) as a white solid. LC/MS System B: R_t = 3.26 min, m/z (ES^+) = 261 ((M+H) for $C_{13}H_{16}N_4O_2$).

3-(2-amino-6-methyl-pyrimidin-4-ylamino)-phenol hydrochloride (2Q):



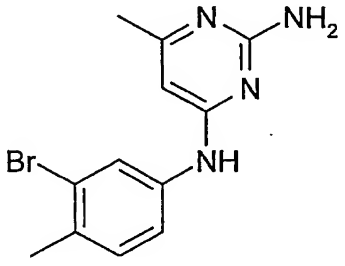
(123 mg, 49 %) as a white solid. LC/MS System B: R_t = 2.77 min, m/z (ES^+) = 217 ((M+H) for $C_{11}H_{12}N_4O$).

N^4-indan-4-yl-6-methyl-pyrimidine-2,4-diamine hydrochloride (2R):



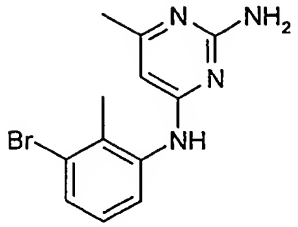
(182 mg, 66 %) as a beige coloured solid. LC/MS System B: R_t = 4.03 min, m/z (ES^+) = 241 ((M+H) for $C_{14}H_{16}N_4$).

N^4-(3-bromo-4-methyl-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2S):



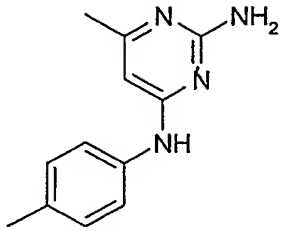
(270 mg, 82 %) as a fawn coloured solid. LC/MS System B: R_t =4.39 min, m/z (ES^+) = 293, 295 ((M+H) for $C_{12}H_{13}BrN_4$).

N^4-(3-bromo-2-methyl-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2T):



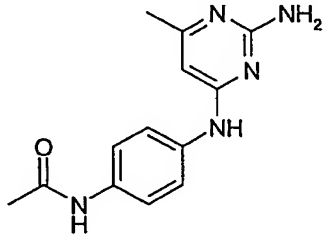
(289 mg, 88 %) as a white solid. LC/MS System B: R_t = 4.12 min, m/z (ES^+) = 293, 295 ((M+H) for $C_{12}H_{13}BrN_4$).

6-methyl-N^4-*p*-tolyl-pyrimidine-2,4-diamine hydrochloride (2U):



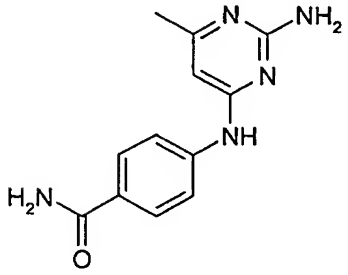
(203 mg, 81 %) as pale yellow crystalline needles. LC/MS System B: R_t = 3.71 min, m/z (ES^+) = 215 ((M+H) for $C_{12}H_{14}N_4$).

N-[4-(2-amino-6-methyl-pyrimidin-4-ylamino)-phenyl]-acetamide hydrochloride (2V):



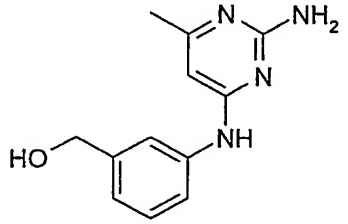
(152 mg, 52 %) as a pink solid. LC/MS System B: R_t = 2.82 min, m/z (ES^+) = 258 ((M+H) for $C_{13}H_{15}N_5O$).

4-(2-amino-6-methyl-pyrimidin-4-ylamino)-benzamide hydrochloride (2W):



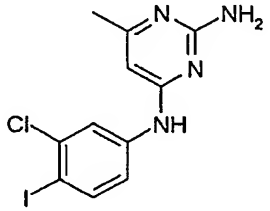
(239 mg, 85 %) as a white solid. LC/MS System B: R_t = 2.50 min, m/z (ES^+) = 244 ((M+H) for $C_{12}H_{13}N_5O$).

[3-(2-amino-6-methyl-pyrimidin-4-ylamino)-phenyl]-methanol hydrochloride (2X):



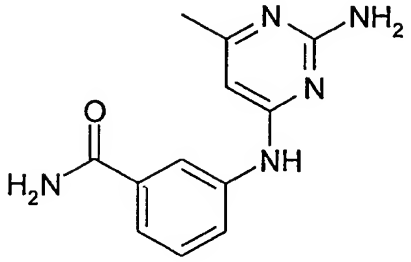
(138 mg, 52 %) as a cream coloured solid. LC/MS System B: R_t = 2.67 min, m/z (ES^+) = 231 ((M+H) for $C_{12}H_{14}N_4O$).

N^4-(3-chloro-4-iodo-phenyl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (2Y):



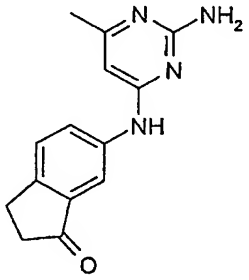
(321 mg, 81 %) as a pale yellow solid. LC/MS System B: R_t = 4.63 min, m/z (ES^+) = 361 ((M+H) for $C_{11}H_{10}ClIN_4$).

3-(2-amino-6-methyl-pyrimidin-4-ylamino)-benzamide hydrochloride (2Z):



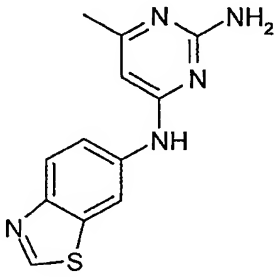
(178 mg, 64 %) as a pale pink solid. LC/MS System B: R_t = 2.46 min (weak), m/z (ES^+) = 244 ((M+H) for $C_{12}H_{13}N_5O$).

6-(2-amino-6-methyl-pyrimidin-4-ylamino)-indan-1-one hydrochloride (2AA):



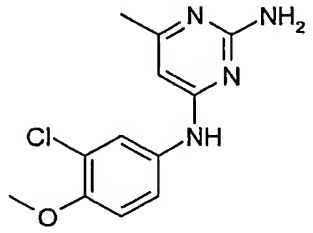
(205 mg, 71 %) as a tan coloured solid. LC/MS System B: R_t = 3.16 min, m/z (ES^+) = 255 ((M+H) for $C_{14}H_{14}N_4O$).

N^4-benzothiazol-6-yl-6-methyl-pyrimidine-2,4-diamine hydrochloride (2AB):



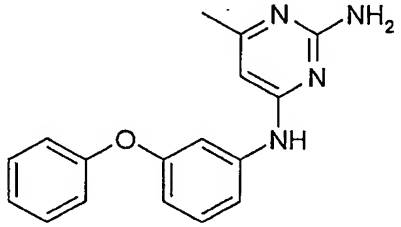
(246 mg, 84 %) as a pale yellow solid. LC/MS System B: R_t = 3.19 min, m/z (ES^+) = 258 ((M+H) for $C_{12}H_{11}N_5S$).

N^4-(3-chloro-4-methoxy-phenyl)-6-methyl-pyrimidine-2,4-diamine, hydrochloride (2AC):



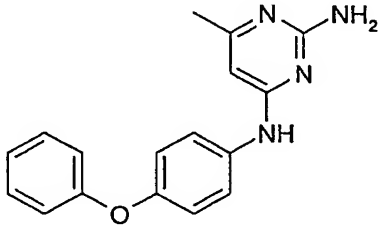
(188 mg, 62 %) as a lilac solid. LC/MS System B: R_t = 3.91 min, m/z (ES^+) = 265 ((M+H) for $C_{12}H_{13}ClN_4O$).

6-methyl-N^4-(3-phenoxy-phenyl)-pyrimidine-2,4-diamine hydrochloride (2AD):



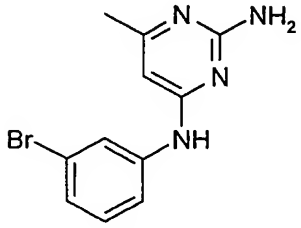
(234 mg, 71 %) as a tan coloured solid. LC/MS System B: R_t = 5.40 min, m/z (ES^+) = 293 ((M+H) for $C_{17}H_{16}N_4O$).

6-methyl-N^4-(4-phenoxy-phenyl)-pyrimidine-2,4-diamine hydrochloride (2AE):



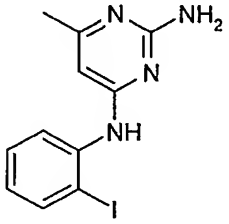
(214 mg, 65 %) as a pale pink solid. LC/MS System B: R_t = 5.57 min, m/z (ES^+) = 293 ((M+H) for $C_{17}H_{16}N_4O$).

N^4-(3-bromo-phenyl)-6-methyl-pyrimidine-2,4-diamine trifluoroacetic acid (2AF):



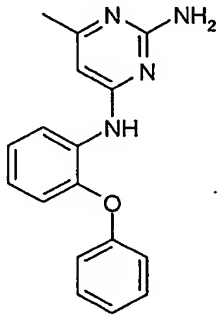
was purified by RP-HPLC to give the title compound (24 mg, 6 %) as a pale pink solid. LC/MS System B: R_t = 4.19 min, m/z (ES^+) = 279, 281 ((M+H) for $C_{11}H_{11}BrN_4$).

N^4-(2-iodo-phenyl)-6-methyl-pyrimidine-2,4-diamine (2AG):



trifluoroacetic acid was purified by RP-HPLC to give the title compound (137 mg, 31 %) as a tan coloured solid. LC/MS System B: R_t = 3.57 min, m/z (ES^+) = 327 ((M+H) for $C_{11}H_{11}IN_4$).

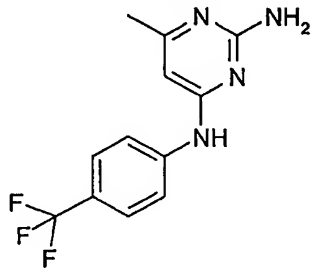
6-methyl-N^4-(2-phenoxy-phenyl)-pyrimidine-2,4-diamine trifluoroacetic acid (2AH):



was purified by RP-HPLC to give the title compound (40 mg,

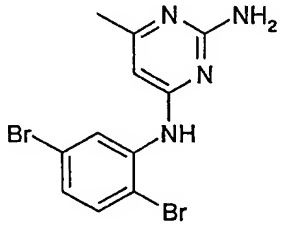
10 %) as a beige coloured solid. LC/MS System B: R_t = 4.90 min, m/z (ES^+) = 293 ((M+H) for $C_{17}H_{16}N_4O$).

6-methyl-N^4-(4-trifluoromethyl-phenyl)-pyrimidine-2,4-diamine trifluoroacetic acid (2AI):



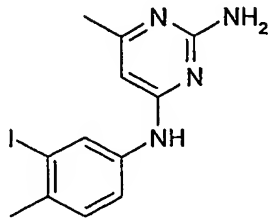
was purified by RP-HPLC to the title compound (62 mg, 16 %) as a give a pale fawn coloured solid. LC/MS System B: R_t = 4.65 min, m/z (ES^+) = 269 ((M+H) for $C_{12}H_{11}F_3N_4$).

N^4-(2,5-dibromo-phenyl)-6-methyl-pyrimidine-2,4-diamine trifluoroacetic acid (2AJ):



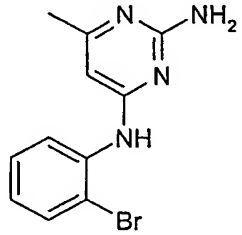
was purified by RP-HPLC to give the title compound (10 mg, 2 %) as a tan coloured solid. LC/MS System A: R_t = 2.05 min, m/z (ES^+) = 359 ((M+H) for $C_{11}H_{10}Br_2N_4$).

N^4-(3-iodo-4-methyl-phenyl)-6-methyl-pyrimidine-2,4-diamine trifluoroacetic acid (2AK):



was purified by RP-HPLC to give the title compound (16 mg, 4 %) as a white solid. LC/MS System A: R_t = 2.15 min, m/z (ES^+) = 341 ((M+H) for $C_{12}H_{13}IN_4$).

N^4-(2-bromo-phenyl)-6-methyl-pyrimidine-2,4-diamine (2AM)



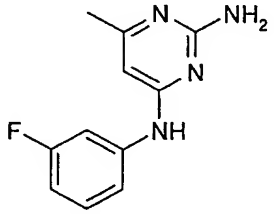
In a Microwave vial (5 mL) was placed 2-amino-4-chloro-6-methylpyrimidine (143 mg), 2-bromoaniline (Compound 1AM, 88 μL) and water (3 mL). The vessel was sealed with a crimped septum cap, and placed in the microwave cavity. The vial was heated to 165 °C for 10 minutes, after this time the vial was allowed to cool to room temperature. The reaction mixture was treated with solid sodium carbonate (106 mg) and then diluted with water (15 mL), the aqueous solution was then extracted with ethyl acetate (3 x 20 mL), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give the title compound (117 mg, 42 %) as a white solid. LC/MS System B: R_t = 3.22 min, m/z (ES^+) = 279, 281 ((M+H) for $C_{11}H_{11}BrN_4$).

Similarly, replacing 2-bromoaniline with other compounds of

formula (1):
3-fluoroaniline (Compound 1AN);
N-(4-aminophenyl)-*N*-methylacetamide (Compound 1AO); and
5-bromo-2-methyl-phenylamine (Compound 1AP);

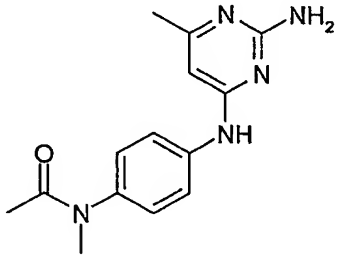
and following the procedures of preparation of Compound 2AL above, the following compounds of the formula (2) were prepared:

N^4-(3-fluoro-phenyl)-6-methyl-pyrimidine-2,4-diamine (2AN):



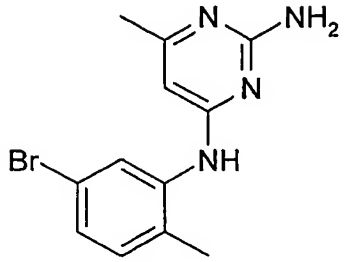
(123 mg, 56 %) as a white solid. LC/MS System B: R_t = 3.49 min, m/z (ES^+) = 219 ((M+H) for $C_{11}H_{11}FN_4$).

N-[4-(2-amino-6-methyl-pyrimidin-4-ylamino)-phenyl]-N-methyl-acetamide (2AO):



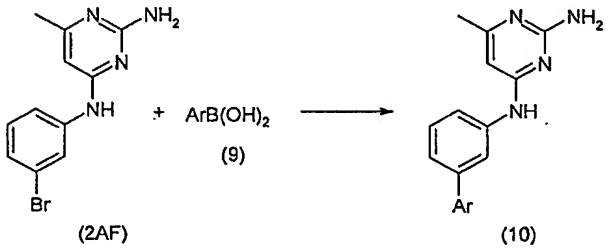
(294 mg, 94 %) as a fawn coloured solid. LC/MS System B: R_t = 2.92 min, m/z (ES^+) = 272 ((M+H) for $C_{14}H_{17}N_5O$).

N^4-(5-bromo-2-methyl-phenyl)-6-methyl-pyrimidine-2,4-diamine (2AP):

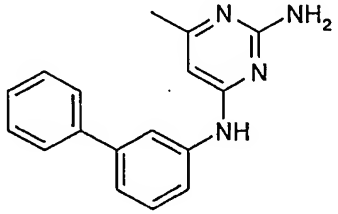


(262 mg, 89 %) as a white solid. LC/MS System B: R_t = 3.92 min, m/z (ES^+) = 293, 295 ((M+H) for $C_{12}H_{13}BrN_4$).

Example 1(a)(ii): Synthesis of N^4-biaryl-6-methyl-pyrimidine-2,4-diamines



N^4-biphenyl-3-yl-6-methyl-pyrimidine-2,4-diamine trifluoroacetic acid (10A)



In a microwave vial (5 mL) was placed N^4-(3-bromo-phenyl)-6-methyl-pyrimidine-2,4-diamine (2AF, 279 mg), benzeneboronic acid (9A, 122 mg), palladium (0) tetrakis(triphenylphosphine) (46mg), 2M cesium carbonate (2 mL), and *N,N*-dimethylformamide (3 mL). The vial was heated

to 140°C for 3 minutes, allowed to cool to room temperature and then filtered through a short pad of hyflo to remove palladium residues. The filtrate was concentrated under reduced pressure and partitioned between water (25 mL) and ethyl acetate (25 mL), the aqueous was further extracted with ethyl acetate (2 x 25mL). The combined ethyl acetate extracts were dried over magnesium sulfate, and filtered, the filtrate was concentrated under reduced pressure to afford an oil. Purification by RP-HPLC to give the title compound (185 mg, 47 %) a cream solid. LC/MS System B: R_t = 4.92 min, m/z (ES^+) = 277 ((M+H) for $C_{17}H_{16}N_4$).

Compounds 10B - 10J

Similarly, replacing benzeneboronic acid with other compounds of formula (9):

3,4-dimethoxybenzeneboronic acid (9B);

3-acetylbenzeneboronic acid (9C);

3-pyridylboronic acid (9D);

3-methylbenzeneboronic acid (9E);

2-methoxybenzeneboronic acid (9F);

3-hydroxybenzeneboronic acid (9G);

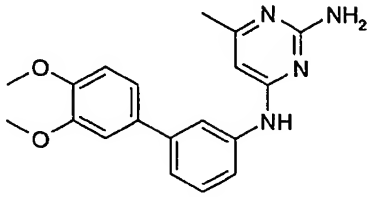
4-(*N*,*N*-dimethylaniline)boronic acid (9H);

3-acetamidobenzeneboronic acid (9I);

4-(methanesulphonyl)benzeneboronic acid acid (9J);

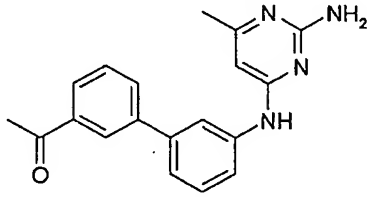
and following the procedures of preparation of 10A above, the following compounds of the formula (10) were prepared:

N^4-(3',4'-dimethoxy-biphenyl-3-yl)-6-methyl-pyrimidine-2,4-diamine trifluoroacetic acid (10B):



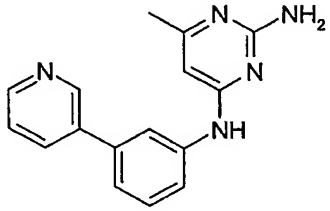
(81 mg, 45 %) as a white solid. LC/MS System B: R_t = 5.17 min, m/z (ES^+) = 337 ((M+H) for $C_{19}H_{20}N_4O_2$).

1-[3'-(2-amino-6-methyl-pyrimidin-4-ylamino)-biphenyl-3-yl]-ethanone trifluoroacetic acid (10C):



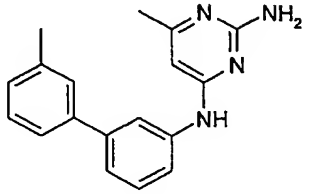
(47 mg, 27 %) as a cream solid. LC/MS System B: R_t = 5.24 min, m/z (ES^+) = 319 ((M+H) for $C_{19}H_{18}N_4O$).

6-methyl-N^4-(3-pyridin-3-yl-phenyl)-pyrimidine-2,4-diamine bis trifluoroacetic acid (10D):



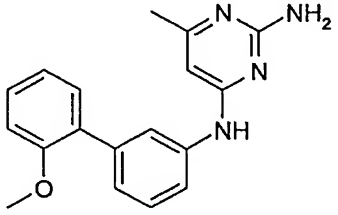
(39 mg, 20 %) as a white solid. LC/MS System B: R_t = 2.88 min, m/z (ES^+) = 278 ((M+H) for $C_{16}H_{15}N_5$).

6-methyl-N^4-(3'-methyl-biphenyl-3-yl)-pyrimidine-2,4-diamine trifluoroacetic acid (10E):



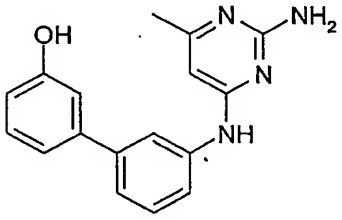
(96 mg, 59 %) as a cream solid. LC/MS System B: R_t = 5.71 min, m/z (ES^+) = 291 ((M+H) for $C_{18}H_{18}N_4$).

N^4-(2'-methoxy-biphenyl-3-yl)-6-methyl-pyrimidine-2,4-diamine trifluoroacetic acid (10F):



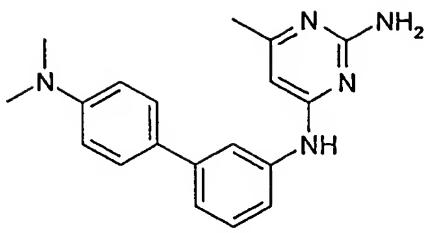
(93 mg, 55 %) as a cream solid. LC/MS System B: R_t = 5.13 min, m/z (ES^+) = 307 ((M+H) for $C_{18}H_{18}N_4O$).

3'-(2-amino-6-methyl-pyrimidin-4-ylamino)-biphenyl-3-ol trifluoroacetic acid (10G):



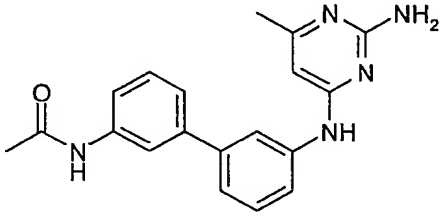
(11 mg, 7 %) as a white solid. LC/MS System B: R_t = 4.50 min, m/z (ES^+) = 293 ((M+H) for $C_{17}H_{16}N_4O$).

N^4-(4'-dimethylamino-biphenyl-3-yl)-6-methyl-pyrimidine-2,4-diamine bis trifluoroacetic acid (10H):



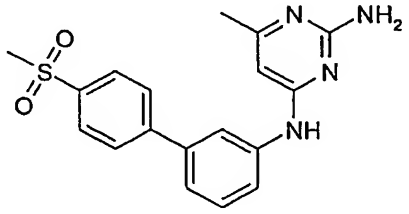
(81 mg, 37 %) as a white solid. LC/MS System B: R_t = 4.20 min, m/z (ES^+) = 320 ((M+H) for $C_{19}H_{21}N_5$).

N-[3'-(2-amino-6-methyl-pyrimidin-4-ylamino)-biphenyl-3-yl]-acetamide hydrochloride (10I):



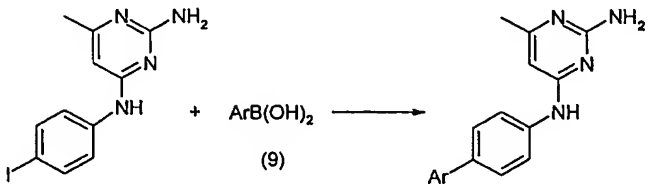
was purified by RP-HPLC, which required a small amount of concentrated hydrochloric acid to aid solubility in acetonitrile / water mixture, upon standing a solid precipitated. The solid was collected by filtration and dried to give the title compound (75 mg, 51 %) as a pale pink solid. LC/MS System B: R_t = 4.83 min, m/z (ES^+) = 334 ((M+H) for $C_{19}H_{19}N_5O$).

N^4-(4'-methanesulfonyl-biphenyl-3-yl)-6-methyl-pyrimidine-2,4-diamine hydrochloride (10J):



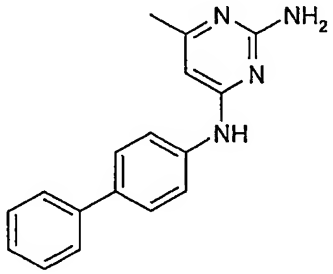
was purified by RP-HPLC, which required a small amount of concentrated hydrochloric acid to aid solubility in acetonitrile / water mixture, upon standing a solid

precipitated. The solid was collected by filtration and dried to give the title compound (78 mg, 50 %) as a grey solid. LC/MS System B: R_t = 4.39 min, m/z (ES^+) = 355 ((M+H) for $C_{18}H_{18}N_4O_2S$).



(2E) (11)

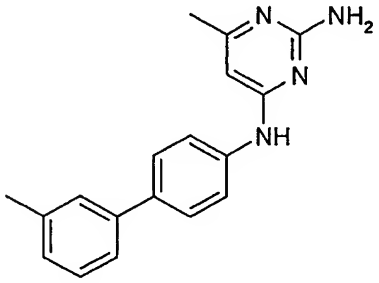
N^4-biphenyl-4-yl-6-methyl-pyrimidine-2,4-diamine trifluoroacetic acid (11A)



In a microwave vial (5 mL) was placed N^4-(4-iodo-phenyl)-6-methyl-pyrimidine-2,4-diamine (2E, 362 mg), benzeneboronic acid (9A, 122 mg), palladium (0) tetrakis(triphenylphosphine) (46 mg), 2M cesium carbonate (2 mL), and *N,N*-dimethylformamide (3 mL). The vial was heated to 140°C for 3 minutes, allowed to cool to room temperature and then filtered through a short pad of hyflo to remove palladium residues. The filtrate was concentrated under reduced pressure and partitioned between water (25 mL) and ethyl acetate (25 mL), the aqueous was further extracted with ethyl acetate (2 x 25 mL). The combined ethyl acetate extracts were dried over magnesium sulfate, and filtered, the filtrate was concentrated under reduced pressure to

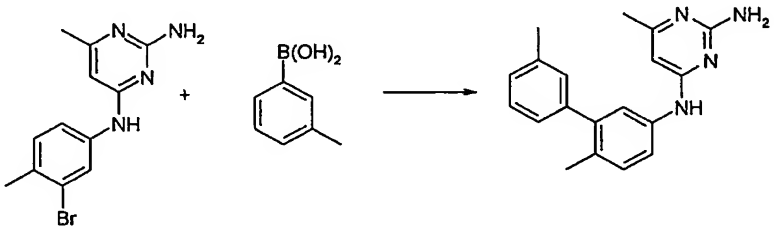
afford an oil. Purification by RP-HPLC gave the title compound (136 mg, 35 %) as a cream solid. LC/MS System B: R_t = 4.93 min, m/z (ES^+) = 277 ((M+H) for $C_{17}H_{16}N_4$).

6-methyl-N^4-(3'-methyl-biphenyl-4-yl)-pyrimidine-2,4-diamine (11B)



Similarly, replacing benzeneboronic acid with 3-methyl benzeneboronic acid (9E) and following the procedures of preparation of 11A above, the title compound (29.5 mg, 27 %) was isolated as a pale tan coloured solid. LC/MS System B: R_t = 5.38 min, m/z (ES^+) = 291 ((M+H) for $C_{18}H_{18}N_4$).

N^4-(6,3'-dimethyl-biphenyl-3-yl)-6-methyl-pyrimidine-2,4-diamine (12)

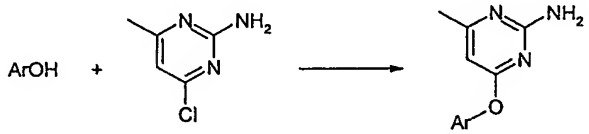


(2S) (9E) (12)

In a microwave vial (5 mL) was placed N^4-(3-bromo-4-methyl-phenyl)-6-methyl-pyrimidine-2,4-diamine (2S, 100 mg), 3-methyl benzeneboronic acid (9E, 45 mg), palladium (0) tetrakis(triphenylphosphine) (20 mg), 2M cesium carbonate (800 µL), and *N,N*-dimethylformamide (3 mL). The vial was heated to 140°C for 3 minutes, allowed to cool to room

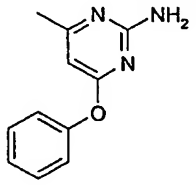
temperature and then filtered through a short pad of hyflo to remove palladium residues. The filtrate was concentrated under reduced pressure and partitioned between water (25 mL) and ethyl acetate (25mL), the aqueous was further extracted with ethyl acetate (2 x 25ml). The combined ethyl acetate extracts were dried over magnesium sulfate, and filtered, the filtrate was concentrated under reduced pressure to give crude product. The solid was purified by recrystallisation with ethyl acetate to give the title compound (15 mg, 16 %) as a pink solid. LC/MS System B: R_t = 5.43 min, m/z (ES^+) = 305 ((M+H) for $C_{19}H_{20}N_4$).

Example 1(b): Synthesis of 4-methyl-6-aryloxy-pyrimidin-2-ylamines



(3) (4)

4-methyl-6-phenoxy-pyrimidin-2-ylamine (4A)



In a Microwave vial (5 mL) was placed 2-amino-4-chloro-6-methylpyrimidine (143 mg), phenol (3A, 94 mg), 2M potassium hydroxide (500 µL) and water (3.5 mL). The vessel was sealed with a crimped septum cap, and placed in the microwave cavity. The vial was heated to 165°C for 5 minutes, after this time the vial was allowed to cool to room temperature, whereupon a solid precipitated. The solid was collected by filtration and dried in a heated desiccator to give the title compound (180 mg, 89 %) as a white solid.

LC/MS System B: R_t = 3.07 min, m/z (ES^+) = 202 ((M+H) for $C_{11}H_{11}N_3O$).

Compounds 4B – 4E

Similarly, replacing phenol with other compounds of formula (3):

Naphthalene-1-ol (3B)

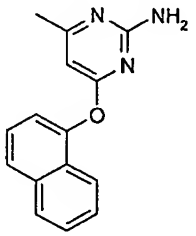
biphenyl-3-ol (3C);

biphenyl-2-ol (3D);

biphenyl-4-ol (3E);

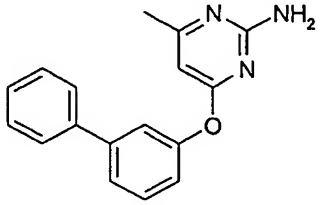
and following the procedures of preparation of 4A above, the following compounds of the formula (4) were prepared:

4-methyl-6-(naphthalen-1-yloxy)-pyrimidin-2-ylamine (4B)



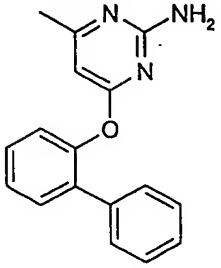
(119 mg, 33 %) as a yellow solid. LC/MS System B: R_t = 5.04 min, m/z (ES^+) = 252 ((M+H) for $C_{15}H_{13}N_3O$).

4-(biphenyl-3-yloxy)-6-methylpyrimidin-2-ylamine (4C)



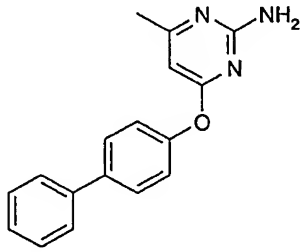
(109 mg, 28 %) as a pale yellow solid. LC/MS System B: R_t = 5.88 min, m/z (ES^+) = 278 ((M+H) for $C_{17}H_{15}N_3O$).

4-(biphenyl-2-yloxy)-6-methylpyrimidin-2-ylamine (4D)



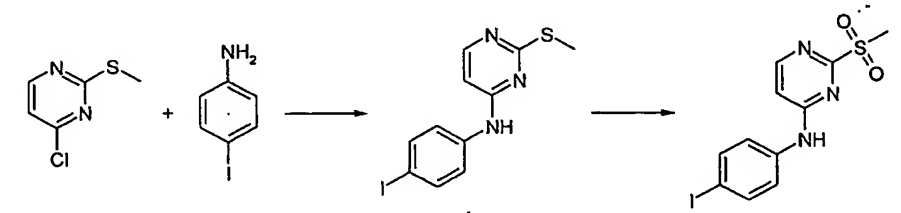
(65 mg, 17 %) as a pink solid. LC/MS System B: R_t = 5.52 min, m/z (ES^+) = 278 ((M+H) for $C_{17}H_{15}N_3O$).

4-(biphenyl-4-yloxy)-6-methylpyrimidin-2-ylamine (4E)

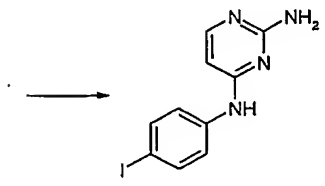


(70 mg, 25 %) as a white solid. LC/MS System B: R_t = 6.02 min, m/z (ES^+) = 278 ((M+H) for $C_{17}H_{15}N_3O$).

Example 1(c): Synthesis of N^4-(4-iodo-phenyl)-pyrimidin-2,4-diamine



13 1E 14 15



16

(4-Iodo-phenyl)-(2-methylsulfanyl-pyrimidin-4-yl)-amine hydrochloride (14)

In a Microwave vial (5 mL) was placed 4-chloro-2-methylsulfanyl-pyrimidine (13, 124 mg), 4-iodoaniline (Compound 1E, 177 mg) and water (2 mL). The vessel was sealed with a crimped septum cap, and placed in the microwave cavity. The vial was heated at 165 °C for 10 minutes, after this time the vial was allowed to cool to room temperature, whereupon the title compound (236 mg, 80 %) precipitated from solution as a white solid. LC/MS System B: R_t = 3.02 min, m/z (ES^+) = 344 ((M+H) for $C_{11}H_{10}IN_3S$).

(4-Iodo-phenyl)-(2-methanesulfonyl-pyrimidin-4-yl)-amine (15)

A mixture of (4-Iodo-phenyl)-(2-methylsulfanyl-pyrimidin-4-yl)-amine hydrochloride (14, 100 mg), *meta*-chloroperoxybenzoic acid (160 mg) and chloroform was stirred at room temperature for 18 hours. The mixture was diluted with chloroform (8 mL), washed with a saturated solution of sodium thiosulfate (10 mL) and a saturated solution of sodium carbonate (10 mL). The organics were dried over magnesium sulfate and the solvent removed under reduced pressure to afford the title compound (81 mg, 81 %) as a peach solid. LC/MS System B: R_t = 3.10 min, m/z (ES^+) = 374 ((M+H) for $C_{11}H_{10}IN_3O_2S$).

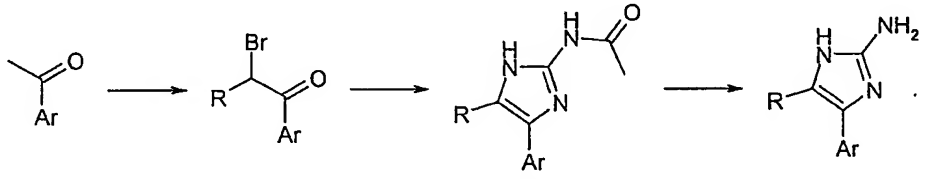
N^4-(4-Iodo-phenyl)-pyrimidine-2,4-diamine (16)

In a bomb at -80 °C was added (4-Iodo-phenyl)-(2-methanesulfonyl-pyrimidin-4-yl)-amine (15, 100 mg), and liquid ammonia (10 mL). The vessel was sealed, allowed to warm to room temperature and then heated at 90 °C at 400 psi for 18 hours. The valve was opened at -80 °C and the liquid

ammonia was allowed to evaporate as the bomb slowly warmed to room temperature. The residue was dissolved in ethyl acetate, washed with a saturated solution of sodium hydrogen carbonate and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford the title compound (37 mg, 45 %) as an orange solid. LC/MS System B: R_t = 4.20 min, m/z (ES^+) = 313 ((M+H) for $C_{10}H_9IN_4$).

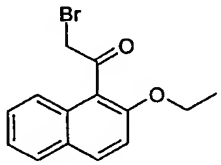
Example 2

Example 2(a): Synthesis of optionally 5-substituted, 4-aryl-1H-imidazol-2-ylamines



(101) (102) (103) (104)

2-Bromo-1-(2-ethoxy-naphthalen-1-yl)-ethanone (102A)



To a solution of 1-(2-ethoxy-naphthalen-1-yl)-ethanone (Compound 101A, 26 g) in tetrahydrofuran (200 mL) at 0°C was added phenyl trimethylammonium tribromide (50 g). The mixture was stirred at 0°C for 10 minutes and then at room temperature for 4.5 hours. The mixture was washed with water (200 mL) and the aqueous phase was extracted with diethyl ether. The combined organics were washed with water (200 mL), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to afford a dark green sticky solid. The sticky solid was triturated with

diethyl ether (100 mL) and filtered to give 2,2-dibromo-1-(2-ethoxy-naphthalen-1-yl)-ethanone (12.6 g, 35 %) as an off-white solid. The filtrate was evaporated to a dark green oil and purified by column chromatography, elution with 40 % to 60 % dichloromethane in cyclohexane, affording 2-bromo-1-(2-ethoxy-naphthalen-1-yl)-ethanone (15.8 g, 44 %) as an off-white solid. ^{1}H NMR ($CDCl_3$): 1.45 (3H, m), 4.2 (2H, m), 4.5 (2H, m), 7.2 (1H, m), 7.4 (1H, m), 7.5 (1H, m), 7.8 (2H, m), 7.9 (1H, m).

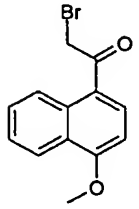
Compounds 102B – 102M

Similarly, replacing 1-(2-ethoxy-naphthalen-1-yl)-ethanone with other compounds of formula (101):

1-(4-methoxy-naphthalen-1-yl)-ethanone (101B);
1-(2-methoxy-naphthalen-1-yl)-ethanone (101C);
1-biphenyl-2-yl-ethanone (101D);
1-(1-methoxy-naphthalen-2-yl)-ethanone (101E);
1-(4-fluoro-naphthalen-1-yl)-ethanone (101F);
1-(7-bromo-naphthalen-1-yl)-ethanone (101G);
1-(5-bromo-naphthalen-1-yl)-ethanone (101H);
1-naphthalen-1-yl-propan-1-one (101I);
1-(2-methoxy-naphthalen-1-yl)-propan-1-one (101J);
3-methyl-1-naphthalen-1-yl-butan-1-one (101K);
1-benzo[b]thiophen-4-yl-ethanone (101L);
1-(2-benzyloxy-naphthalen-1-yl)-ethanone (101M);

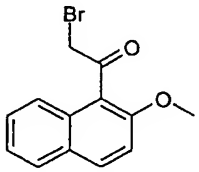
and following the procedures of preparation of Compound 102A above, the following compounds of the formula (102) were prepared:

2-Bromo-1-(4-methoxy-naphthalen-1-yl)-ethanone (102B):



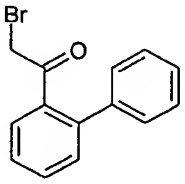
(3.0 g, 86 %) as a yellow / green oil, ^{1}H NMR ($CDCl_3$): 4.05 (3H, s), 4.5 (2H, s), 6.8 (1H, d, J = 8.2 Hz), 7.5 (1H, ddd, J = 8.4, 7.0, 1.2 Hz), 7.6 (1H, ddd, J = 8.6, 7.0, 1.5 Hz), 8.0 (1H, d, J = 8.4 Hz), 8.3 (1H, d, J = 8.4 Hz), 8.9 (1H, d, J = 8.6 Hz).

2-Bromo-1-(2-methoxy-naphthalen-1-yl)-ethanone (102C):



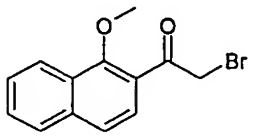
(5.25 g, 75 %) as a yellow oil, ^{1}H NMR (DMSO-D6): 4.0 (3H, s), 4.75 (2H, s), 7.45 (1H, ddd, J = 8.1, 6.7, 1.3 Hz), 7.55-7.65 (3H, m), 7.95 (1H, d, J = 8.1 Hz), 8.2 (1H, d, J = 9.2 Hz);

1-Biphenyl-2-yl-2-bromo-ethanone (102D):



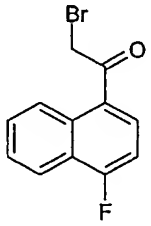
(2.7 g, 48 %), ^{1}H NMR (DMSO-D6): 4.4 (2H, s), 7.25-7.30 (2H, m), 7.35-7.45 (4H, m), 7.45 (1H, td, J = 7.6, 1.3 Hz), 7.6 (1H, td, J = 7.6, 1.4 Hz), 7.65 (1H, dd, J = 7.7, 1.3 Hz).

2-Bromo-1-(1-methoxy-naphthalen-2-yl)-ethanone (102E):



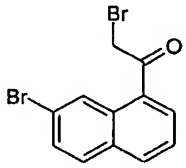
(13.2 g, 65 %) as a white solid, ^{1}H NMR (DMSO-D6): 3.95 (3H, s), 4.95 (2H, s), 7.60-7.75 (4H, m), 7.95-7.80 (1H, m), 8.15-8.20 (1H, m).

2-Bromo-1-(4-fluoro-naphthalen-1-yl)-ethanone (102F):



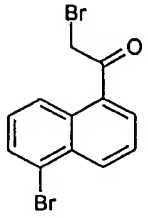
(5.7 g, 100 %) as a colourless oil, ^{1}H NMR ($CDCl_3$): 4.5 (2H, s), 7.15 (1H, dd, J = 9.7, 8.1 Hz), 7.55-7.70 (2H, m), 7.9-8.0 (1H, m), 8.15 (1H, m), 8.75 (1H, m).

2-Bromo-1-(7-bromo-naphthalen-1-yl)-ethanone (102G):



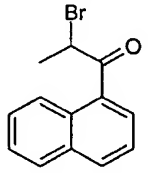
(29.7 g, 96 %) as an off-white solid, ^{1}H NMR ($CDCl_3$): 4.55 (2H, s), 7.5 (1H, m), 7.6 (1H, m), 7.75 (1H, d, J = 8.8 Hz), 7.95-8.0 (2H, m), 8.9 (1H, d, J = 1.3 Hz).

2-Bromo-1-(5-bromo-naphthalen-1-yl)-ethanone (102H):



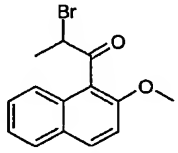
(10.9 g, 100 %) as an off-white solid, ^{1}H NMR ($CDCl_3$): 4.5 (2H, s), 7.4 (1H, dd, J = 8.9, 7.6 Hz), 7.6 (1H, dd, J = 8.7, 7.1 Hz), 7.8-7.9 (2H, m), 8.5 (2H, m).

2-Bromo-1-naphthalen-1-yl-propan-1-one (102I):



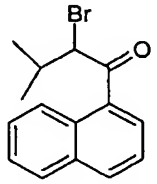
(6.0 g, 78 %) as an off-white solid, ^{1}H NMR ($CDCl_3$): 1.95 (3H, d, J = 6.6 Hz), 5.35 (1H, q, J = 6.6 Hz), 7.45-7.60 (3H, m), 7.85-7.90 (2H, m), 8.0 (1H, d, J = 8.4 Hz), 8.4 (1H, m).

2-Bromo-1-(2-methoxy-naphthalen-1-yl)-propan-1-one (102J):



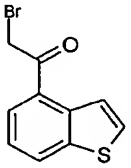
(2.87 g, 25 %) as a cream solid, ^{1}H NMR ($CDCl_3$): 1.9 (3H, d, J = 6.7 Hz), 3.95 (3H, s), 5.25 (1H, q, J = 6.7 Hz), 7.25 (1H, d, J = 9.2 Hz), 7.35 (1H, m), 7.5 (1H, m), 7.75 (2H, m), 7.9 (1H, d, J = 9.0 Hz).

2-Bromo-3-methyl-1-naphthalen-1-yl-butan-1-one (102K):



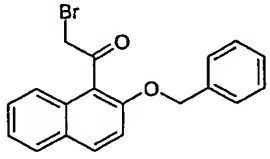
(3.9 g, 60 %) as a yellow oil, ^{1}H NMR ($CDCl_3$): 1.1 (3H, d, J = 6.6 Hz), 1.2 (3H, d, J = 6.6 Hz), 2.5 (1H, m), 5.0 (1H, d, J = 8.3 Hz), 7.5 (1H, dd, J = 8.1, 7.2 Hz), 7.55 (1H, ddd, J = 8.1, 6.9, 1.2 Hz), 7.6 (1H, ddd, J = 8.5, 6.9, 1.5 Hz), 7.8-7.9 (2H, m), 8.0 (1H, d, J = 8.3 Hz), 8.4 (1H, d, J = 8.8 Hz).

1-Benzo[b]thiophen-4-yl-2-bromo-ethanone (102L):



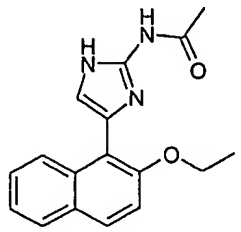
(6.8 g, 92 %) as an orange oil, ^{1}H NMR ($CDCl_3$): 4.6 (2H, s), 7.4 (1H, t, J = 7.8 Hz), 7.65 (1H, d, J = 5.7 Hz), 7.95 (1H, dd, J = 7.8, 0.9 Hz), 8.1 (1H, dt, J = 7.8, 0.9 Hz), 8.3 (1H, dd, J = 5.7, 0.9 Hz).

1-(2-Benzyloxy-naphthalen-1-yl)-2-bromo-ethanone (102M):



(10.2 g, 74 %) as a white solid, ^{1}H NMR (DMSO-D6): 4.7 (2H, s), 5.35 (2H, s), 7.3-7.6 (9H, m), 7.9 (1H, d, J = 8.1 Hz), 8.05 (1H, d, J = 9.0 Hz).

N-[4-(2-Ethoxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103A)



A solution of 2-bromo-1-(2-ethoxy-naphthalen-1-yl)-ethanone (Compound 102A, 4.0 g), 1-acetylguanidine (4.1 g) and N,N-dimethylformamide (24 mL) was split equally between 8 microwave vials. These vials were heated at 180°C and treated with microwave irradiation for 180 seconds. The contents from each of the vials were combined in a round-bottomed flask and the N,N-dimethylformamide was removed under reduced pressure. The brown residue precipitated from a mixture of ethyl acetate (30 mL) and water (30 mL) to afford N-[4-(2-ethoxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (1.4 g, 35 %) as a cream solid. ^{1}H NMR (DMSO-D6): 1.25 (3H, m), 2.05 (3H, s), 4.1 (2H, m), 6.95 (1H, m), 7.3-8.3 (6H, m), 11.2-11.6 (2H, m). Mass Spectrum (m/z): 296 $(M+H)^+$.

Compounds 103B - 103P

Similarly, replacing 2-bromo-1-(2-ethoxy-naphthalen-1-yl)-ethanone with other compounds of the formula (102):

2-bromo-1-(4-methoxy-naphthalen-1-yl)-ethanone (102B);
2-bromo-1-(2-methoxy-naphthalen-1-yl)-ethanone (102C);
1-biphenyl-2-yl-2-bromo-ethanone (102D);
2-bromo-1-(1-methoxy-naphthalen-2-yl)-ethanone (102E);
2-bromo-1-(4-fluoro-naphthalen-1-yl)-ethanone (102F);
2-bromo-1-(7-bromo-naphthalen-1-yl)-ethanone (102G);
2-bromo-1-(5-bromo-naphthalen-1-yl)-ethanone (102H);
2-bromo-1-naphthalen-1-yl-propan-1-one (102I);

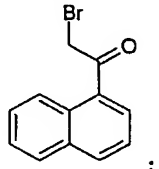
2-bromo-1-(2-methoxy-naphthalen-1-yl)-propan-1-one (102J);

2-bromo-3-methyl-1-naphthalen-1-yl-butan-1-one (102K);

1-benzo[b]thiophen-4-yl-2-bromo-ethanone (102L);

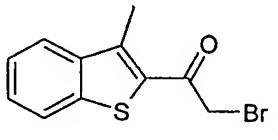
1-(2-benzyloxy-naphthalen-1-yl)-2-bromo-ethanone (102M);

2-bromo-1-naphthalen-1-yl-ethanone (102N)



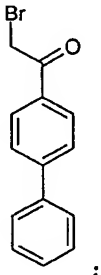
;

2-bromo-1-(3-methyl-benzo[b]thiophen-2-yl)-ethanone (102O)



;

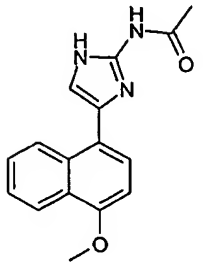
1-biphenyl-4-yl-2-bromo-ethanone (102P)



;

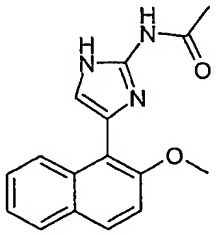
and following the procedures of preparation of Compound 103A above, the following compounds of the formula (103) were prepared:

N-[4-(4-Methoxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103B):



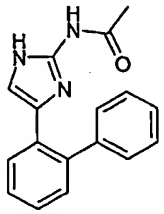
was purified by column chromatography, eluting with 5 % methanol in dichloromethane, affording a pale brown solid. Recrystallisation from industrial methylated spirits gave the title compound (0.25 g, 29 %) as a beige solid. ^{1}H NMR (DMSO-D6): 2.05 (3H, s), 3.9 (3H, s), 6.95-7.00 (2H, m), 7.45-7.55 (3H, m), 8.15 (1H, m), 8.65 (1H, m), 11.2 (1H, br s), 11.6 (1H, br s). Mass Spectrum (m/z): 282 $(M+H)^+$.

N-[4-(2-Methoxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103C):



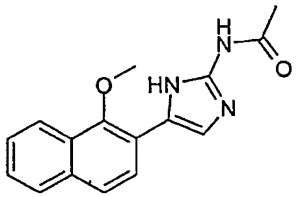
was purified by column chromatography, eluting with 1 to 2 % methanol in dichloromethane, affording a peach solid. Recrystallisation from a mixture of ethanol and chloroform gave the title compound (42 mg, 16 %). ^{1}H NMR (DMSO-D6): 2.05 (3H, s), 3.95 (3H, s), 6.95-7.00 (2H, s), 7.45-7.50 (2H, m), 7.55 (1H, d, J = 7.55 Hz), 8.15 (1H, m), 8.6 (1H, d, J = 7.5 Hz), 11.2 (1H, br s), 11.6 (1H, br s). Mass Spectrum (m/z): 282 $(M+H)^+$.

N-(4-Biphenyl-2-yl-1H-imidazol-2-yl)-acetamide (103D):



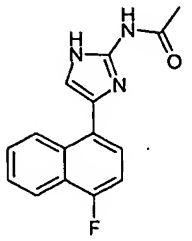
was purified by column chromatography, eluting with 70 % ethyl acetate in cyclohexane, affording the title compound (171 mg, 43 %) as a cream crystalline solid. ^{1}H NMR ($CDCl_3$): 1.9 (3H, s), 6.4 (1H, br s), 7.25-7.75 (9H, m), 10.4 (1H, br s), 10.6 (1H, br s). Mass Spectrum (m/z): 282 $(M+H)^+$.

N-[4-(1-Methoxy-naphthalen-2-yl)-1H-imidazol-2-yl]-acetamide (103E):



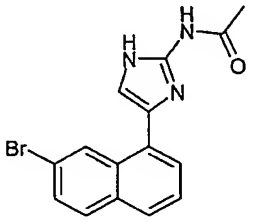
was purified by column chromatography affording an orange solid. Recrystallisation from ethanol gave the title compound (100 mg, 18 %) as a white solid. ^{1}H NMR (DMSO-D6): 2.05 (3H, s), 3.75 (3H, s), 7.35 (1H, s), 7.4 (1H, t, J = 7.2 Hz), 7.5 (1H, t, J = 7.5 Hz), 7.65 (1H, d, J = 8.6 Hz), 7.85 (1H, d, J = 8.2 Hz), 8.0 (1H, d, J = 8.6 Hz), 8.1 (1H, d, J = 8.2 Hz), 11.2 (1H, br s), 11.7 (1H, br s). Mass Spectrum (m/z): 282 $(M+H)^+$.

N-[4-(4-Fluoro-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103F):



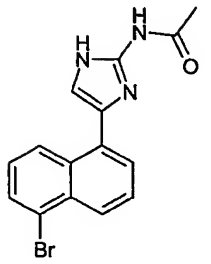
was purified by column chromatography affording a white solid. Recrystallisation from a mixture of hexane and acetone gave the title compound (632 mg, 63 %) as a white solid. ^{1}H NMR ($CDCl_3$): 2.15 (3H, s), 7.0 (1H, s), 7.15-7.20 (1H, m), 7.45-7.55 (3H, m), 8.15 (1H, m), 8.4 (1H, m), 11.05 (1H, br s), 12.55 (1H, br s). Mass Spectrum (m/z): 270 $(M+H)^+$.

N-[4-(7-Bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103G):



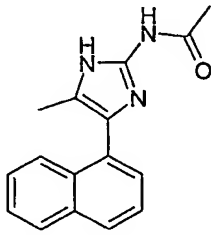
was purified by column chromatography affording the title compound (0.78 g, 26 %) as a green solid. ^{1}H NMR (DMSO-D6): 1.95 (3H, s), 7.15 (1H, d, J = 1.5 Hz), 7.5 (1H, d, J = 8.1, 7.2 Hz), 7.6 (1H, dd, J = 8.8, 2.2 Hz), 7.65 (1H, dd, J = 7.2, 1.1 Hz), 7.8 (1H, d, J = 8.1 Hz), 7.85 (1H, d, J = 8.6 Hz), 9.05 (1H, d, J = 2.0 Hz), 11.3 (1H, br s), 11.8 (1H, br s). Mass Spectrum (m/z): 230 $(M+H)^+$.

N-[4-(5-Bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103H):



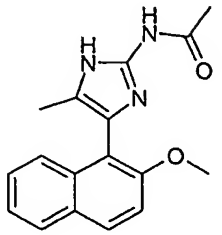
was purified by column chromatography affording a pale brown solid. Recrystallisation from acetone to gave the title compound (150 mg, 15 %) as a cream solid. ^{1}H NMR (DMSO-D6): 2.05 (3H, s), 7.15 (1H, s), 7.4 (1H, m), 7.6 (1H, m), 7.75 (1H, d, J = 7.0 Hz), 7.85 (1H, d, J = 7.2 Hz), 8.05 (1H, d, J = 8.3 Hz), 8.6 (1H, d, J = 8.6 Hz), 11.3 (1H, br s), 11.8 (1H, br s). Mass Spectrum (m/z): 330/332 $(M+H)^+$.

N-(5-Methyl-4-naphthalen-1-yl-1H-imidazol-2-yl)-acetamide (103I):



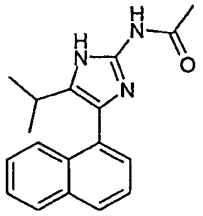
was purified by column chromatography, eluting with 1 to 2 % methanol in dichloromethane, affording the title compound (120 mg, 24 %) as a cream solid. ^{1}H NMR (DMSO-D6): 2.05 (3H, s), 2.1 (3H, s), 7.35-7.50 (4H, m), 7.8-7.9 (2H, m), 8.25 (1H, d, J = 7.0 Hz), 11.05 (1H, br s), 11.55 (1H, br s). Mass Spectrum (m/z): 266 $(M+H)^+$.

N-[4-(2-Methoxy-naphthalen-1-yl)-5-methyl-1H-imidazol-2-yl]-acetamide (103J):



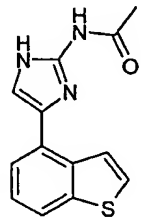
was purified by column chromatography, eluting with 50 and 75 % ethyl acetate in dichloromethane, affording the title compound (210 mg, 7 %) as an orange solid. ^{1}H NMR (DMSO-D6): 1.85 (3H, s), 2.0 (3H, s), 3.8 (3H, s), 7.3-7.6 (3H, m), 7.8-8.0 (2H, m), 11.0 (1H, br s), 11.4 (1H, br s). Mass Spectrum (m/z): 296 $(M+H)^+$.

N-(5-Isopropyl-4-naphthalen-1-yl-1H-imidazol-2-yl)-acetamide (103K):



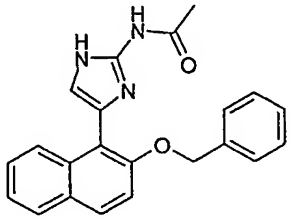
was purified by column chromatography, eluting with 30, 40 and 75 % ethyl acetate in cyclohexane, affording the title compound (196 mg, 6 %) as a fawn solid. ^{1}H NMR (DMSO-D6): 1.1 (6H, m), 2.0 (4H, m), 7.35 (4H, m), 7.85-8.05 (3H, m), 11.0-11.3 (2H, m). Mass Spectrum (m/z): 294 $(M+H)^+$.

N-(4-Benzo[b]thiophen-4-yl-1H-imidazol-2-yl)-acetamide (103L):



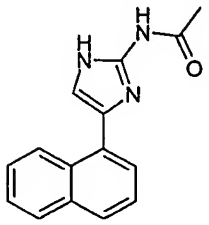
was purified by trituration with diethyl ether affording the title compound (131 mg, 51 %) as a green solid. ^{1}H NMR (DMSO-D6): 2.05 (3H, s), 7.25 (1H, s), 7.3 (1H, t, J = 7.8 Hz), 7.65 (1H, dd, J = 7.5, 0.7 Hz), 7.7 (1H, d, J = 5.5 Hz), 7.8 (1H, d, J = 7.9 Hz), 8.15 (1H, d, J = 5.5 Hz), 11.2 (1H, br s), 11.7 (1H, br s). Mass Spectrum (m/z): 258 $(M+H)^+$.

N-[4-(2-Benzyloxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103M):



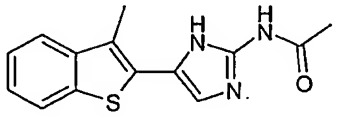
was purified by column chromatography, eluting with 50 % ethyl acetate in cyclohexane, affording the title compound (100 mg, 28 %) as a pale orange foam. ^{1}H NMR (DMSO-D6): 2.05 (3H, s), 5.2 (2H, br s), 7.0 (1H, s), 7.25-7.50 (9H, m), 7.75-8.00 (2H, m), 8.3 (1H, d, J = 7.9 Hz).

N-(4-Naphthalen-1-yl-1H-imidazol-2-yl)-acetamide (103N):



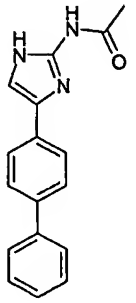
was purified by column chromatography, eluting with 5 and 10 % methanol in dichloromethane, affording a dark purple solid. Recrystallisation from ethanol gave the title compound (0.95 g, 22 %) as a purple solid. ^{1}H NMR (DMSO-D6): 2.1 (3H, s), 7.15 (1H, d, J = 1.8 Hz), 7.50-7.55 (3H, m), 7.7 (1H, m), 7.8 (1H, d, J = 8.0 Hz), 7.9 (1H, m), 8.75 (1H, m), 11.3 (1H, br s), 11.8 (1H, br s). Mass Spectrum (m/z): 252 $(M+H)^+$.

N-[4-(3-Methyl-benzo[b]thiophen-2-yl)-1H-imidazol-2-yl]-acetamide (103O):



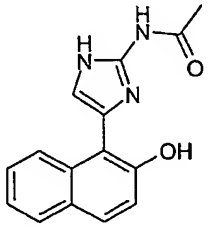
was purified by trituration from dichloromethane affording the title compound (350 mg, 35 %). ^{1}H NMR (DMSO-D6): 2.05 (3H, s), 2.45 (3H, s), 7.05 (1H, s), 7.25 (1H, m), 7.3 (1H, m), 7.7 (1H, d, J = 7.9 Hz), 7.8 (1H, d, J = 7.7 Hz), 11.35 (1H, br s), 11.85 (1H, br s). Mass Spectrum (m/z): 272 $(M+H)^+$.

N-(4-Biphenyl-4-yl-1H-imidazol-2-yl)-acetamide (103P):



was purified by filtration of the reaction mixture affording the title compound as (2.15 g, 53 %) a yellow solid. ^{1}H NMR (DMSO-D6): 2.05 (3H, s), 7.25-7.30 (2H, m), 7.4 (2H, m), 7.55-7.65 (4H, m), 7.75 (2H, m), 11.2 (1H, br s), 11.6 (1H, br s). Mass Spectrum (m/z): 278 $(M+H)^+$.

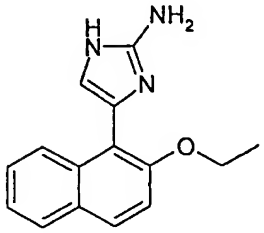
N-[4-(2-hydroxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103Q)



N-[4-(2-Benzyloxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (Compound 103M, 0.9 g) was dissolved in ethanol (100 mL) and then palladium, 10 % on carbon (250 mg) was added. The mixture was stirred under 1 atmosphere of hydrogen for 48 hours. The mixture was filtered through a pad of hyflo and washed with industrial methylated spirits. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography to afford N-[4-(2-hydroxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (300 mg, 44 %). ^{1}H NMR (DMSO-D6): 2.1 (3H, s), 7.1 (1H, d, J = 8.8 Hz), 7.25 (2H, m), 7.45 (1H, t, J = 7.7 Hz), 7.65 (1H, d, J = 9.0 Hz), 7.8 (1H, dd, J = 8.0, 1.2 Hz), 8.25

(1H, d, J = 8.1 Hz). Mass Spectrum (m/z): 268 $(M+H)^+$.

4-(2-Ethoxy-naphthalen-1-yl)-1H-imidazol-2-ylamine (104A)



A solution of N-[4-(2-ethoxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (Compound 103A, 1.4 g), industrial methylated spirits (50 mL), water (10 mL) and concentrated sulfuric acid (1 mL) was heated at 80°C for 9 hours. After cooling to room temperature, the mixture was basified with a 1 % solution of potassium hydroxide in methanol (200 mL). The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water (40 mL), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to afford 4-(2-ethoxy-naphthalen-1-yl)-1H-imidazol-2-ylamine (0.57 g, 47 %) as a brown solid. ^{1}H NMR (DMSO-D6): 1.25 (3H, t, J = 6.9 Hz), 4.1 (2H, q, J = 6.9 Hz), 6.65 (1H, s), 7.25-7.40 (3H, m), 7.75-7.80 (2H, m), 8.25 (1H, m). Mass Spectrum (m/z): 254 $(M+H)^+$.

Compounds 104B – 104F, 104I and 104N

Similarly, replacing N-[4-(2-ethoxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide with other compounds of the formula (103):

N-[4-(4-methoxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103B);

N-[4-(2-methoxy-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103C);

4-biphenyl-2-yl-1H-imidazol-2-ylamine (103D);

N-[4-(1-methoxy-naphthalen-2-yl)-1H-imidazol-2-yl]-acetamide (103E);

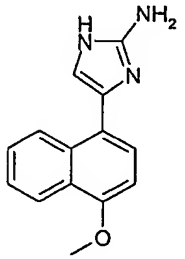
N-[4-(4-fluoro-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103F);

N-(5-methyl-4-naphthalen-1-yl-1H-imidazol-2-yl)-acetamide (103I);

N-(4-naphthalen-1-yl-1H-imidazol-2-yl)-acetamide (103N);

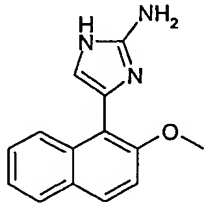
and following the procedures of preparation of Compound 104A above, the following compounds of the formula (104) were prepared:

4-(4-Methoxy-naphthalen-1-yl)-1H-imidazol-2-ylamine (104B):



was purified by column chromatography, eluting with 10 to 50 % methanol in dichloromethane, affording the title compound (17 mg, 10 %) as a purple solid. ^{1}H NMR ($CDCl_3$): 3.85 (3H, s), 6.4 (1H, s), 7.2-7.4 (4H, m), 7.95 (1H, m), 8.2 (1H, m). Mass Spectrum (m/z): 240 $(M+H)^+$.

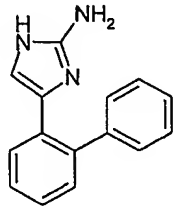
4-(2-Methoxy-naphthalen-1-yl)-1H-imidazol-2-ylamine (104C):



(20 mg, 83 %) as a purple / brown solid. ^{1}H NMR ($CDCl_3$): 3.85 (3H, s), 6.8 (1H, s), 7.25-7.35 (2H, m), 7.4 (1H, m),

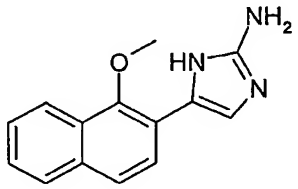
7.75 (2H, m), 8.55 (1H, d, J = 8.6 Hz). Mass Spectrum (m/z): 240 $(M+H)^+$.

2-Biphenyl-2-yl-1H-imidazol-4-ylamine (104D):



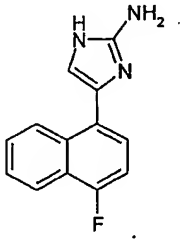
was purified by column chromatography, eluting with 10 % industrial methylated spirits in cyclohexane, affording the title compound (51 mg, 44 %). ^1H NMR ($CDCl_3$): 6.0 (1H, s), 7.2-7.3 (8H, m), 7.55 (1H, m). Mass Spectrum (m/z): 236 $(M+H)^+$.

4-(1-Methoxy-naphthalen-2-yl)-1H-imidazol-2-ylamine (104E):



(30 mg, 35 %) as a brown solid. ^1H NMR (DMSO-D6): 3.75 (3H, s), 7.1 (1H, s), 7.35 (1H, m), 7.5 (2H, m), 7.6 (1H, d, J = 8.6 Hz), 7.8 (1H, d, J = 7.9 Hz), 8.0 (1H, d, J = 8.3 Hz). Mass Spectrum (m/z): 240 $(M+H)^+$.

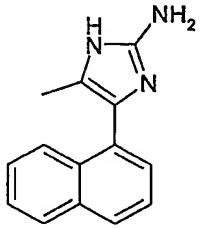
4-(4-Fluoro-naphthalen-1-yl)-1H-imidazol-2-ylamine (104F):



was purified by column chromatography, eluting with 10 %

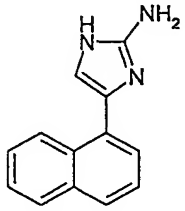
triethylamine in ethanol, affording the title compound (80 mg, 19 %) as a yellow / brown solid. ^{1}H NMR (DMSO-D6): 7.15 (1H, s), 7.4-7.5 (2H, m), 7.55 (1H, m), 7.65 (1H, m), 8.0-8.1 (2H, m). Mass Spectrum (m/z): 228 $(M+H)^+$.

5-Methyl-4-naphthalen-1-yl-1H-imidazol-2-ylamine (104I):



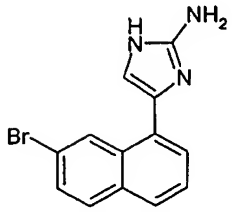
was purified by column chromatography, eluting with 1 % methanol in dichloromethane, affording a yellow solid. Recrystallisation from a mixture a acetone and cyclohexane gave the title compound (3.5 mg, 7 %) as a yellow solid. ^{1}H NMR ($CDCl_3$): 2.0 (3H, s), 7.35-7.45 (4H, m), 7.75 (1H, m), 7.8 (1H, m), 7.95 (1H, m). Mass Spectrum (m/z): 224 $(M+H)^+$.

4-Naphthalen-1-yl-1H-imidazol-2-ylamine (104N):



(0.62 g, 91 %) as a pink solid. ^{1}H NMR (DMSO-D6): 5.35 (2H, br s), 6.9 (1H, s), 7.45-7.50 (3H, m), 7.6 (1H, d, J = 6.6 Hz), 7.7 (1H, d, J = 8.2 Hz), 7.85-7.90 (1H, m), 8.75 (1H, br s). Mass Spectrum (m/z): 210 $(M+H)^+$.

4-(7-Bromo-naphthalen-1-yl)-1H-imidazol-2-ylamine (104G)



A mixture of N-[4-(7-bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (Compound 103G, 0.75 g) and concentrated hydrochloric acid (40 mL) were heated at reflux for 1 hour. On cooling to room temperature a precipitate formed, which was filtered and washed with diethyl ether affording 4-(7-bromo-naphthalen-1-yl)-1H-imidazol-2-ylamine (0.45 g, 61 %) as an off white hydrochloric salt. ^{1}H NMR (DMSO-D6): 7.2 (1H, s), 7.5 (2H, br s), 7.60-7.65 (2H, m), 7.7 (1H, dd, J = 8.8, 2.0 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.0 (1H, m), 8.15 (1H, d, J = 2.0 Hz). Mass Spectrum (m/z): 288 / 290 $(M+H)^+$.

Compound 104H, 104J, 104K, 104O and 104P

Similarly, replacing N-[4-(7-bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide with other compounds of the formula (103):

N-[4-(5-bromo-naphthalen-1-yl)-1H-imidazol-2-yl]-acetamide (103H);

N-[4-(2-methoxy-naphthalen-1-yl)-5-methyl-1H-imidazol-2-yl]-acetamide (103J);

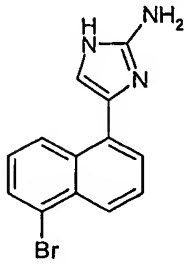
N-(5-isopropyl-4-naphthalen-1-yl-1H-imidazol-2-yl)-acetamide (103K);

N-[4-(3-methyl-benzo[b]thiophen-2-yl)-1H-imidazol-2-yl]-acetamide (103O);

N-(4-biphenyl-4-yl-1H-imidazol-2-yl)-acetamide (103P);

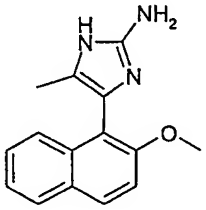
and following the procedures of preparation of Compound 104G above, the following compounds of the formula (104) were prepared:

4-(5-Bromo-naphthalen-1-yl)-1H-imidazol-2-ylamine (104H):



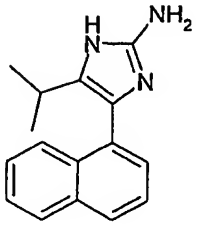
(85 mg, 72 %). ^{1}H NMR (DMSO-D6): 7.2 (1H, s), 7.5 (1H, dd, J = 8.6, 7.5 Hz), 7.55 (2H, br s), 7.65-7.75 (2H, m), 7.95 (1H, dd, J = 7.5, 0.9 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.2 (1H, d, J = 8.3 Hz). Mass Spectrum (m/z): 288 / 290 $(M+H)^+$.

4-(2-Methoxy-naphthalen-1-yl)-5-methyl-1H-imidazol-2-ylamine (104J):



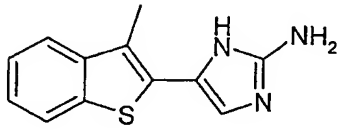
was purified by HPLC, eluting on a gradient of 20 to 80 % acetonitrile in water, using ammonium acetate as buffer, affording the title compound (17 mg, 8 %) as an off-white acetate salt. ^{1}H NMR (DMSO-D6): 1.75 (3H, s), 3.8 (3H, s), 7.3 (1H, ddd, J = 8.1, 6.8, 1.2 Hz), 7.4 (1H, ddd, J = 8.5, 6.8, 1.4 Hz), 7.45 (1H, d, J = 8.9 Hz), 7.6 (1H, d, J = 8.3 Hz), 7.8 (1H, d, J = 8.9 Hz), 7.9 (1H, d, J = 8.9 Hz). Mass Spectrum (m/z): 254 $(M+H)^+$.

5-Isopropyl-4-naphthalen-1-yl-1H-imidazol-2-ylamine (104K):



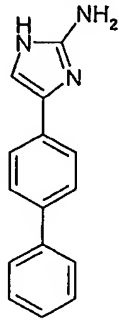
(179 mg, 90 %) as a dark foam hydrochloric salt. ^{1}H NMR (DMSO-D6): 1.1 (6H, d, J = 7.0 Hz), 2.6 (1H, m), 7.3 (2H, br s), 7.5-7.6 (5H, m), 7.7 (1H, m), 8.0 (2H, m). Mass Spectrum (m/z): 252 $(M+H)^+$.

4-(3-Methyl-benzo[b]thiophen-2-yl)-1H-imidazol-2-ylamine (104O):



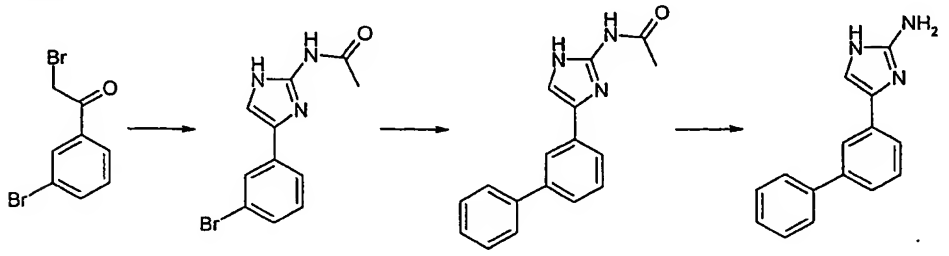
(140 mg, 83 %) as a purple solid. ^{1}H NMR (DMSO-D6): 2.4 (3H, s), 6.85 (1H, s), 7.2 (1H, m), 7.3 (1H, m), 7.65 (1H, d, J = 7.7 Hz), 7.75 (1H, d, J = 7.7 Hz). Mass Spectrum (m/z): 230 $(M+H)^+$.

4-Biphenyl-4-yl-1H-imidazol-2-ylamine (104P):



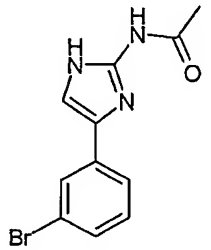
(1.6 g, 83 %) as a peach hydrochloric salt. ^{1}H NMR (DMSO-D6): 7.35 (1H, m), 7.40-7.45 (4H, m), 7.65-7.75 (5H, m). Mass Spectrum (m/z): 236 $(M+H)^+$.

Example 2(b): Synthesis of 4-biphenyl-3-yl-1H-imidazol-2-ylamine



(105) (106) (107) (108)

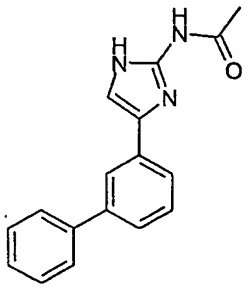
N-[4-(3-bromo-phenyl)-1H-imidazol-2-yl]-acetamide (106)



A solution of 2-bromo-1-(3-bromo-phenyl)-ethanone (105, 6.8 g), 1-acetylguanidine (7.4 g) and *N,N*-dimethylformamide (70 mL) was split equally between 14 microwave vials. These vials were heated at 180°C and treated with microwave irradiation for 180 seconds. The contents from each of the vials were combined in a round-bottomed flask and the *N,N*-dimethylformamide was removed under reduced pressure. The brown residue was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was washed water (2 x 50 mL), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to afford an orange brown / gum. Purification by column chromatography, elution with 10 to 50 % ethyl acetate in cyclohexane, afforded *N*-[4-(3-bromo-phenyl)-1H-imidazol-2-yl]-acetamide (106)(2.95 g, 40 %) as a yellow / green solid. ^{1}H NMR (DMSO-D6): 1.95

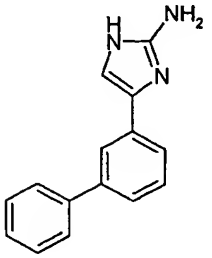
(3H, s), 7.20-7.35 (3H, m), 7.65 (1H, m), 7.85 (1H, m). Mass Spectrum (m/z): 280 /282 $(M+H)^+$.

N-(4-biphenyl-3-yl-1H-imidazol-2-yl)-acetamide (107)



A mixture of *N*-[4-(3-bromo-phenyl)-1H-imidazol-2-yl]-acetamide (Compound 106, 1.0 g), aqueous solution of cesium carbonate (2M, 7.1 mL), phenylboronic acid (0.65 g), 1,4-dioxane (35 mL) and palladium (0) tetrakis(triphenylphosphine) (0.32 g) was heated at 100°C for 30 hours. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (40 mL) and water (40 mL). The organic phase was washed with water (40 mL), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to afford a brown solid. Purification by column chromatography, eluting with 40 % ethyl acetate in dichloromethane, afforded *N*-(4-biphenyl-3-yl-1H-imidazol-2-yl)-acetamide (107)(0.21 g, 22 %) as a fawn solid. ^1H NMR (DMSO-D6): 2.05 (3H, s), 7.30-7.45 (6H, m), 7.65 (3H, m), 7.95 (1H, m). Mass Spectrum (m/z): 278 $(M+H)^+$.

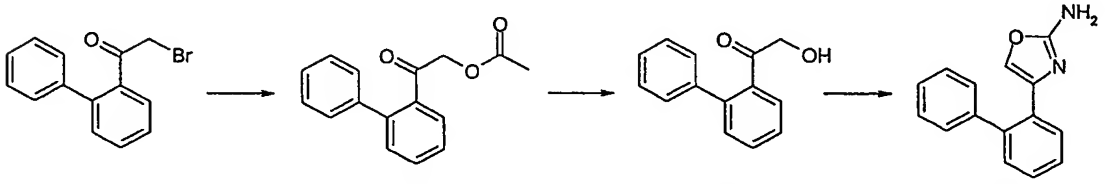
4-biphenyl-3-yl-1H-imidazol-2-ylamine (108)



A mixture of *N*-(4-biphenyl-3-yl-1H-imidazol-2-yl)-acetamide (107, 0.18 g) and concentrated hydrochloric acid (10 mL) were heated at reflux for 1 hour. The concentrated hydrochloric acid was removed under reduced pressure and the residue was purified by HPLC, eluting on a gradient of 30 to 90 % acetonitrile in water, using trifluoroacetic acid as buffer afforded 4-biphenyl-3-yl-1H-imidazol-2-ylamine (108)(33 mg, 22 %) as a white trifluoroacetate salt. ^{1}H NMR (DMSO-D6): 7.35 (1H, m), 7.45-7.50 (4H, m), 7.55-7.65 (4H, m), 7.7 (2H, m), 7.95 (1H, m). Mass Spectrum (m/z): 288 / 290 $(M+H)^+$.

Example 3

Example 3(a): Synthesis of 5-biphenyl-2-yl-oxazol-2-ylamine (203)



200 201 202 203

Acetic acid 2-biphenyl-2-yl-2-oxo-ethyl ester (201)

A mixture of 1-biphenyl-2-yl-2-bromo-ethanone (Compound 200, 2.9 g), N,N-dimethylformamide (60 mL) and sodium acetate

(0.87 g), was heated at 90°C for 16 hours. The N,N-dimethylformamide was removed under reduced pressure and the residue was partitioned between brine (100 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organics were dried over magnesium sulfate. The solvent was removed under reduced pressure to give a dark orange gum, which was purified by column chromatography, eluting with dichloromethane, to afford acetic acid 2-biphenyl-2-yl-2-oxo-ethyl ester (2.6 g, 96 %) as an orange gum. ^{1}H NMR (DMSO-D6) 2.0 (3H, s), 4.85 (2H, s), 7.25-7.40 (6H, m), 7.5 (1H, m), 7.6 (1H, m), 7.65 (1H, m).

1-Biphenyl-2-yl-2-hydroxy-ethanone (202)

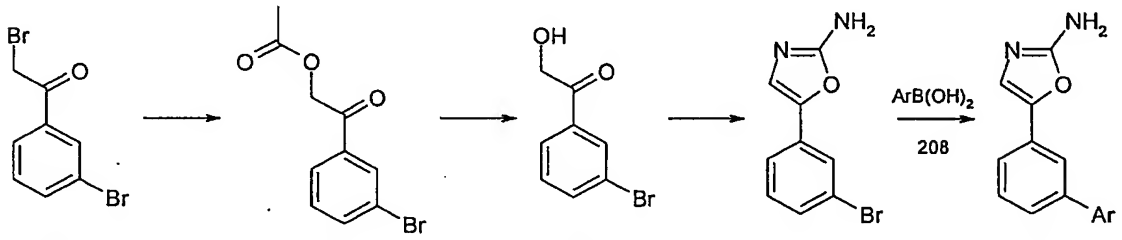
A mixture of acetic acid 2-biphenyl-2-yl-2-oxo-ethyl ester (Compound 201, 2.6 g), industrial methylated spirits (20 mL) and 1 M hydrochloric acid (15 mL) was heated at reflux for 2 hours. The solvent was removed under reduced pressure and the crude material was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organics were washed with a saturated solution of sodium carbonate (50 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure give a pale yellow oil, which was purified by column chromatography, eluting with dichloromethane, to afford 1-biphenyl-2-yl-2-hydroxy-ethanone (0.83 g, 38 %) as a colourless oil. ^{1}H NMR (DMSO-D6) 4.15 (2H, d, J = 5.9 Hz), 5.1 (1H, t, J = 5.9 Hz), 7.25-7.55 (9H, m).

5-biphenyl-2-yl-oxazol-2-ylamine (203)

In a microwave vial was placed 1-biphenyl-2-yl-2-hydroxy-ethanone (Compound 202, 0.83 g), cyanamide (0.49 g) and N,N-

dimethylformamide (5 mL). The vessel was equipped with a stirrer bar, sealed with a crimped septum cap, and placed in the microwave cavity. The vial was heated at 250°C for 10 minutes, after this time the vial was allowed to cool to room temperature, and the resultant mixture was concentrated to dryness under reduced pressure. The residue was purified by column chromatography, eluting with tert-butyl methyl ether, to afford 5-biphenyl-2-yl-oxazol-2-ylamine (0.18 g, 19 %) as an orange solid. LC/MS System A: Rt = 2.45 min, m/z (ES^+) = 237 ((M+H) for C15H12N2O). ^1H NMR (DMSO-D6) 6.7 (2H, br s), 7.15 (1H, m), 7.20-7.25 (3H, m), 7.35-7.40 (5H, m), 7.45 (1H, dd, J = 7.9, 1.1 Hz).

Example 3(b) : Synthesis of 5-biphenyl-3-yl-oxazol-2-ylamines



204 205 206 207 209

Acetic acid 2-(3-bromo-phenyl)-2-oxo-ethyl ester (205)

A mixture of 2-bromo-1-(3-bromo-phenyl)-ethanone (Compound 204, 19.1 g), sodium acetate (5.6 g) and N,N-dimethylformamide (250 mL) was heated at 90°C for 16 hours. The N,N-dimethylformamide was removed under reduced pressure and the residue was partitioned between brine and ethyl acetate. The aqueous layer was extracted with ethyl acetate and the combined organics were dried over magnesium sulfate. The solvent was removed under reduced pressure to give acetic acid 2-(3-bromo-phenyl)-2-oxo-ethyl ester (16.9 g, 96 %) as a dark orange. ^1H NMR ($CDCl_3$) 2.2 (3H, s), 5.25 (2H, s), 7.35 (1H, t, J = 7.9 Hz), 7.7 (1H, m), 7.8 (1H, m),

8.0 (1H, m).

1-(3-Bromo-phenyl)-2-hydroxy-ethanone (206)

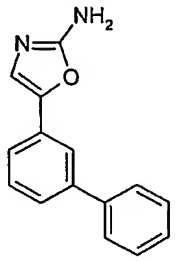
A mixture of acetic acid 2-(3-bromo-phenyl)-2-oxo-ethyl ester (Compound 205, 16.9 g), industrial methylated spirits (110 mL) and 1 M hydrochloric acid (85 mL) was heated at reflux for 2 hours. The solvent was removed under reduced pressure and the residue was partitioned between water (300 mL) and ethyl acetate (300 mL). The organic layer was washed with water (300 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford 1-(3-bromo-phenyl)-2-hydroxy-ethanone (13.1 g, 93 %) as a yellow solid. ^{1}H NMR ($CDCl_3$) 5.25 (2H, s), 7.35 (1H, t, J = 7.9 Hz), 7.7 (1H, m), 7.8 (1H, m), 8.0 (1H, m).

5-(3-Bromophenyl)-oxazol-2-ylamine (207)

A solution of 1-(3-bromo-phenyl)-2-hydroxy-ethanone (Compound 206, 13.1 g), cyanamide (7.7 g), and N,N-dimethylformamide (130 mL) was split equally between 26 microwave vials. The vessels were equipped with a stirrer bar, sealed with a crimped septum cap, and placed in the microwave cavity. The vials were heated at 200°C for 10 minutes, after this time the vials were allowed to cool to room temperature, and the resultant mixtures were combined in a round bottom flask, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate (200 mL) and water (200 mL), the organic layer was washed with brine (200 mL) and the combined organics were dried over magnesium sulfate. The solvent was removed under reduced pressure to give a brown solid, which was purified by column chromatography, eluting with 50 % ethyl acetate in dichloromethane, to afford 4-(3-bromophenyl)-oxazol-2-ylamine (3.57 g, 24 %) as a beige solid. LC/MS System B: Rt

= 4.77 min, m/z (ES^+) = 239,241 ((M+H) for $C_9H_7BrN_2O$). ^1H NMR (DMSO-D6) 6.9 (2H, br s), 7.25-7.30 (3H, m), 7.4 (1H, m), 7.6 (1H, m).

5-Biphenyl-3-yl-oxazol-2-ylamine (209A)



In a microwave vial was placed 4-(3-bromophenyl)-oxazol-2-ylamine (Compound 207, 200 mg), benzeneboronic acid (Compound 208A, 157 mg), palladium (0) tetrakis (triphenylphosphine) (38 mg), 2M cesium carbonate (1.65 mL), and N,N-dimethylformamide (3.0 mL). The vial was heated to 100°C for 3 minutes, allowed to cool to room temperature and then filtered through a short pad of hyflo. The filtrate was concentrated under reduced pressure and partitioned between water (20 mL) and dichloromethane (20 mL). The organic layer was washed with water (20 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give an orange solid, which was recrystallised from a mixture of industrial methylated spirits and cyclohexane to afford 5-biphenyl-3-yl-oxazol-2-ylamine (70 mg, 35 %) as a peach solid. LC/MS System B: Rt = 6.06 min, m/z (ES^+) = 237 ((M+H) for $C_{15}H_{12}N_2O$). ^1H NMR (DMSO-D6) 6.8 (2H, br s), 7.25 (1H, s), 7.35 (1H, m), 7.40-7.45 (5H, m), 7.6-7.7 (3H, m).

Compounds 209B – 209M

Similarly, replacing benzeneboronic acid (208A) with other compounds of formula (208):

3-methylbenzeneboronic acid (208B);

3-hydroxybenzeneboronic acid (208C);

3-cyanobenzeneboronic acid (208D);

2-chlorobenzeneboronic acid (208E);

3-pyridylboronic acid (208F);

2-methoxybenzeneboronic acid (208G);

3-acetylbenzeneboronic acid (208H);

3-(trifluoromethyl)benzeneboronic acid (208I);

4-fluorobenzeneboronic acid (208J);

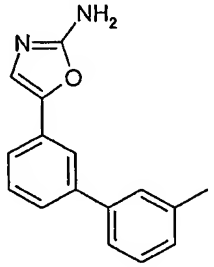
3,5-dimethylbenzeneboronic acid (208K);

4-ethylbenzeneboronic acid (208L);

3-isopropylbenzeneboronic acid (208M);

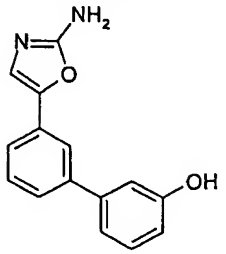
and following the procedures of preparation of Compound 209A above, the following compounds of the formula (209) were prepared:

5-(3'-Methyl-biphenyl-3-yl)-oxazol-2-ylamine (209B):



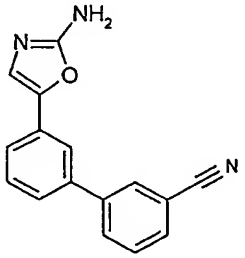
was purified by column chromatography, eluting with 20 to 40 % ethyl acetate in dichloromethane, followed by recrystallisation from a mixture of ethyl acetate and cyclohexane to afford the title compound (29 mg, 12 %) as a white solid, LC/MS System B: Rt = 6.72 min, m/z (ES^+) = 251 ((M+H) for $C_{16}H_{14}N_2O$), 1H NMR (DMSO-D6) 2.35 (3H, m), 6.8 (2H, br s), 7.15 (1H, m), 7.25 (1H, s), 7.3 (1H, t, J = 7.6 Hz), 7.40-7.45 (5H, m), 7.65 (1H, m).

3'-(2-Amino-oxazol-5-yl)-biphenyl-3-ol (209C):



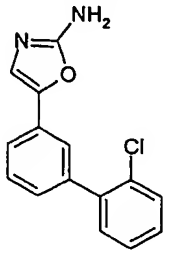
was purified by column chromatography, eluting with 20 to 40 % ethyl acetate in dichloromethane, followed by recrystallisation from a mixture of ethyl acetate and cyclohexane to afford the title compound (36 mg, 14 %) as an off-white solid, LC/MS System B: Rt = 4.89 min, m/z (ES^+) = 253 ((M+H) for $C_{16}H_{14}N_2O$), ^1H NMR (DMSO-D6) 6.75 (1H, dd, J = 8.1, 1.5 Hz), 6.8 (2H, br s), 7.0 (1H, m), 7.05 (1H, m), 7.20-7.25 (2H, m), 7.35-7.40 (3H, m), 7.6 (1H, m), 9.5 (1H, br s).

3'-(2-Amino-oxazol-5-yl)-biphenyl-3-carbonitrile (209D):



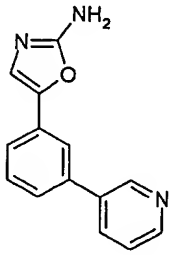
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (27 mg, 7 %) as an off-white solid, LC/MS System B: Rt = 5.88 min, m/z (ES^+) = 262 ((M+H) for $C_{16}H_{11}N_3O$), ^1H NMR (DMSO-D6) 6.85 (2H, br s), 7.25-7.30 (2H, m), 7.45-7.55 (3H, m), 7.65 (1H, t, J = 7.8 Hz), 7.75 (1H, m), 7.8 (1H, m), 8.0 (1H, m).

5-(2'-Chloro-biphenyl-3-yl)-oxazol-2-ylamine (209E):



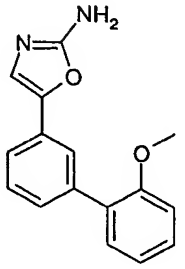
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute to afford the title compound (0.26 g, 7 %) as a white solid, LC/MS System B: Rt = 6.70 min, m/z (ES^+) = 271 ((M+H) for $C_{15}H_{11}ClN_2O$), ^1H NMR (DMSO-D6) 7.3 (1H, m), 7.40-7.45 (4H, m), 7.5-7.6 (6H, m).

5-(3-Pyridin-3-yl-phenyl)-oxazol-2-ylamine (209F):



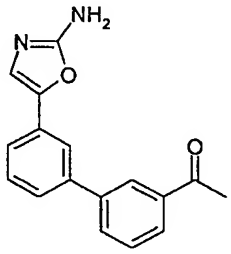
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (18 mg, 5 %) as a white solid, LC/MS System B: Rt = 2.59 min, m/z (ES^+) = 238 ((M+H) for $C_{14}H_{11}N_3O$), ^1H NMR (DMSO-D6) 7.6 (2H, m), 7.8 (1H, m), 7.95-8.00 (2H, m), 8.05 (1H, s), 8.7 (1H, d, J = 8.1 Hz), 8.8 (1H, d, J = 4.4 Hz), 9.2-9.3 (3H, m).

5-(2'-Methoxy-biphenyl-3-yl)-oxazol-2-ylamine trifluoroacetic acid (209G):



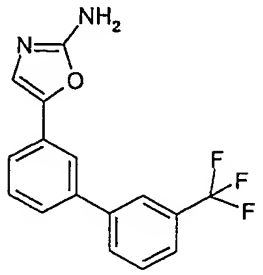
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (20 mg, 5 %) as a white solid, LC/MS System B: Rt = 6.05 min, m/z (ES^+) = 267 ((M+H) for $C_{16}H_{14}N_2O_2$), ^1H NMR (DMSO-D6) 3.75 (3H, s), 7.0 (1H, td, J = 7.5, 1.1 Hz), 7.1 (1H, dd, J = 8.3, 0.9 Hz), 7.25 (1H, dd, J = 7.5, 1.8 Hz), 7.30-7.45 (4H, m), 7.6 (2H, m).

1-[3'-(2-Amino-oxazol-5-yl)-biphenyl-3-yl]-ethanone, trifluoroacetic acid (209H):



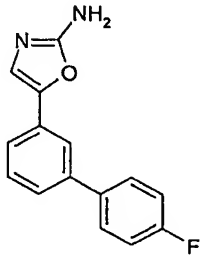
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (180 mg, 5 %) as a white solid, LC/MS System B: Rt = 4.96 min, m/z (ES^+) = 279 ((M+H) for $C_{17}H_{14}N_2O_2$), ^1H NMR (DMSO-D6) 2.6 (3H, s), 7.3 (1H, m), 7.4 (1H, m), 7.55 (2H, m), 7.6-7.7 (3H, m), 7.81 (1H, m), 7.9-8.0 (2H, m), 8.15 (1H, m).

5-(3'-Trifluoromethyl-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (209I):



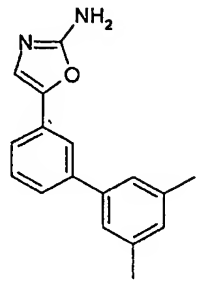
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (108 mg, 32 %) as a white solid, LC/MS System B: Rt = 6.67 min, m/z (ES^+) = 305 ((M+H) for $C_{16}H_{11}F_3N_2O$), ^1H NMR (DMSO-D6) 7.50-7.75 (6H, m), 7.85 (1H, m), 7.95-8.15 (4H, m).

5-(4'-Fluoro-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (209J):



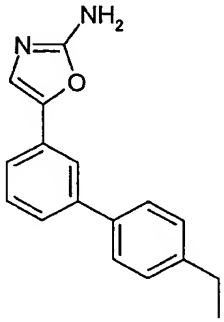
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (34 mg, 2 %) as a white solid, LC/MS System B: Rt = 5.68 min, m/z (ES^+) = 255 ((M+H) for $C_{15}H_{11}FN_2O$), ^1H NMR (DMSO-D6) 7.25-7.30 (2H, m), 7.45-7.55 (3H, m), 7.65-7.75 (4H, m).

5-(3',5'-Dimethyl-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (209K):



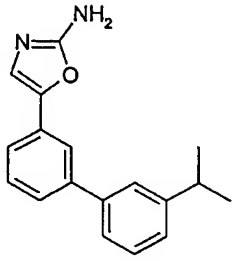
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (80 mg, 25 %) as a white solid, LC/MS System B: Rt = 6.61 min, m/z (ES^+) = 265 ((M+H) for $C_{17}H_{16}N_2O$), ^1H NMR (DMSO-D6) 2.3 (6H, s), 7.0 (1H, s), 7.25 (2H, m), 7.45-7.55 (3H, m), 7.65 (1H, s), 7.7 (1H, m).

5-(4'-Ethyl-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (209L):



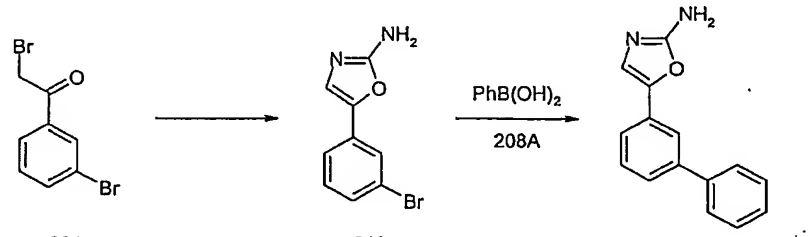
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (15 mg, 5 %) as a white solid, LC/MS System B: Rt = 6.66 min, m/z (ES^+) = 265 ((M+H) for $C_{17}H_{16}N_2O$) ^1H NMR (DMSO-D6) 1.2 (3H, t, J = 7.5 Hz), 2.6 (2H, q, J = 7.5 Hz), 7.3 (2H, m), 7.35-7.45 (4H, m), 7.55 (2H, m), 7.7 (1H, m).

5-(3'-Isopropyl-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (209M):



was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (8 mg 2 %) as a white solid, LC/MS System B: Rt = 6.84 min, m/z (ES^+) = 279 ((M+H) for $C_{18}H_{18}N_2O$), ^1H NMR (DMSO-D6) 1.2 (6H, d, J = 6.8 Hz), 2.9 (1H, m), 7.3 (2H, m), 7.4-7.6 (5H, m), 7.65 (1H, m), 7.75 (1H, m).

Example 3(c): Synthesis of 5-biphenyl-3-yl-oxazol-2-ylamine, trifluoroacetic acid (211)



204 210 211

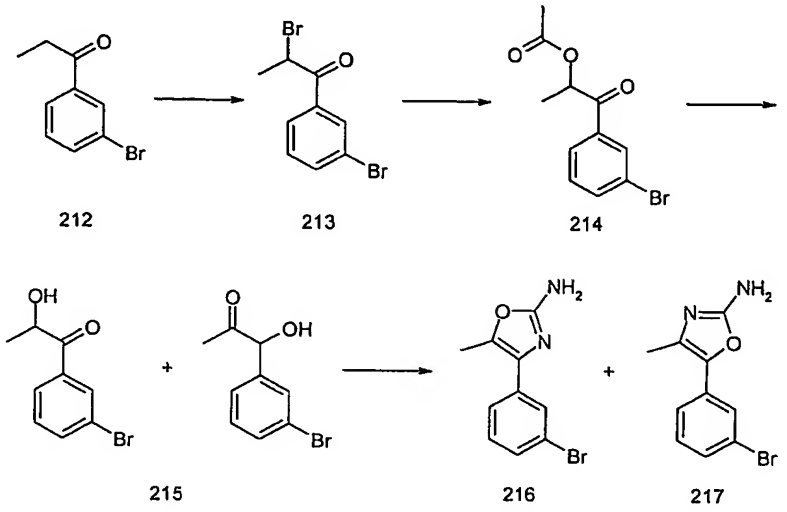
(3-Bromo-phenyl)-oxazol-2-ylamine (210)

A solution of 2-bromo-1-(3-bromo-phenyl)-ethanone (Compound 204, 6.8 g), urea (4.4 g) and N,N-dimethylformamide (70 mL) was split equally between 14 microwave vials. The vessels were equipped with a stirrer bar, sealed with a crimped septum cap, and placed in the microwave cavity. The vials were heated at 180°C for 3 minutes, after this time the vials were allowed to cool to room temperature, and the resultant mixtures were combined in a round bottom flask, and the solvent removed under reduced pressure. The residue

was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was washed with brine (2 x 50 mL), dried over magnesium sulfate and the solvent removed under reduced pressure to give a yellow solid. The crude product was purified by column chromatography, eluting with 5 to 30 % ethyl acetate in cyclohexane, to afford 5-(3-bromo-phenyl)-oxazol-2-ylamine compound (1.1 g, 9 %) as a yellow solid. LC/MS System B: Rt = 5.97 min, m/z (ES^+) = 239, 241 ((M+H) for $C_9H_7BrN_2O$). ^1H NMR (DMSO-D6) 6.7 (2H, br s), 7.25 (1H, t, J = 7.9 Hz), 7.35 (1H, ddd, J = 7.9, 1.9, 1.1 Hz), 7.55 (1H, ddd, J = 7.9, 1.3, 1.1, Hz), 7.75 (1H, t, J = 1.9 Hz), 7.9 (1H, s).

5-Biphenyl-3-yl-oxazol-2-ylamine, trifluoroacetic acid (211)
In a microwave vial was placed 5-(3-bromo-phenyl)-oxazol-2-ylamine (Compound 210, 500 mg), benzeneboronic acid (Compound 208A, 378 mg), palladium (0) tetrakis (triphenylphosphine) (97 mg), 2M cesium carbonate (4.2 mL), and N,N-dimethylformamide (3 mL). The vial was heated at 100°C for 3 minutes, allowed to cool to room temperature and then concentrated under reduced pressure. The residue was partitioned between water (5 mL) and dichloromethane (5 mL). The organic layer was washed with water (5 mL), dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford 5-biphenyl-3-yl-oxazol-2-ylamine, trifluoroacetic acid (39 mg, 5 %) as a white solid. LC/MS System B: Rt = 6.33 min, m/z (ES^+) = 237 ((M+H) for $C_{15}H_{12}N_2O$). ^1H NMR (DMSO-D6) 6.7 (2H, br s), 7.25-7.65 (8H, m), 7.90 (1H, m), 7.95 (1H, s).

Example 3(d): Synthesis of intermediates 4-(3-bromo-phenyl)-5-methyl-oxazol-2-ylamine (216) and 5-(3-bromo-phenyl)-4-methyl-oxazol-2-ylamine (217)



2-Bromo-1-(3-bromo-phenyl)-propan-1-one (213)

To a solution of in 1-(3-bromo-phenyl)-propan-1-one (Compound 212, 25.1 g) 1,2-dimethoxyethane (250 mL) at 0°C was added phenyl trimethylammonium tribromide (47.7 g). The mixture was stirred at 0°C for 10 minutes and then at room temperature for 2 hours. The mixture was diluted with ethyl acetate (300 mL), washed with water (200 mL), dried over magnesium sulfate and the solvent removed under reduced pressure to afford 2-bromo-1-(3-bromo-phenyl)-propan-1-one (33.6 g, 97 %) as an orange oil. ^{1}H NMR ($CDCl_3$) 1.85 (3H, d, J = 6.6 Hz), 5.2 (1H, q, J = 6.6 Hz), 7.35 (1H, t, J = 8.0 Hz), 7.7 (1H, ddd, J = 8.0, 2.0, 1.0 Hz), 7.9 (1H, ddd, J = 8.0, 1.8, 1.0 Hz), 8.1 (1H, t, J = 1.8 Hz).

Acetic acid 2 -(3-bromo-phenyl)-1-methyl-2-oxo-ethyl ester (214)

A mixture of 2-bromo-1-(3-bromo-phenyl)-propan-1-one (Compound 213, 30.1g), sodium acetate (8.4 g) and N,N-dimethylformamide (350 mL) was heated at 90°C for 2 hours.

The N,N-dimethylformamide was removed under reduced pressure and the residue was partitioned between water (300 mL) and dichloromethane (300 mL). The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to afford acetic acid 2-(3-bromo-phenyl)-1-methyl-2-oxo-ethyl ester (25.1 g, 90 %) as a dark orange liquid. ^{1}H NMR ($CDCl_3$) 1.5 (3H, d, J = 7.0 Hz), 2.1 (3H, s), 5.8 (1H, q, J = 7.0 Hz), 7.3 (1H, t, J = 7.9 Hz), 7.7 (1H, ddd, J = 7.9, 1.8, 1.1 Hz), 7.8 (1H, m), 8.0 (1H, t, J = 1.8 Hz).

1-(3-bromo-phenyl)-2-hydroxy-propan-1-one and 1-(3-bromo-phenyl)-1-hydroxy-propan-2-one (215)

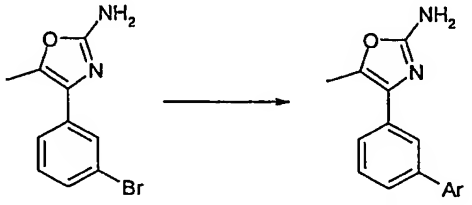
A mixture of acetic acid 2-(3-bromo-phenyl)-1-methyl-2-oxo-ethyl ester (Compound 214, 25.1 g), industrial methylated spirits (150 mL) and 1 M hydrochloric acid (120 mL) was heated at reflux for 2 hours. The solvent was removed under reduced pressure and the crude material was partitioned between water (100 mL) and ethyl acetate (100 mL). The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to afford a 2:1 mixture of 1-(3-bromo-phenyl)-2-hydroxy-propan-1-one and 1-(3-bromo-phenyl)-1-hydroxy-propan-2-one (18.8 g, 89 %) as a dark orange oil. 1H NMR (CDCl3) 1.4 (3H, d, J = 7.0 Hz), 2.1 (3H, s), 3.6 (1H, d, J = 6.4 Hz), 4.3 (1H, d, J = 4.2 Hz), 5.0 (1H, d, J = 4.2 Hz), 5.05 (1H, m), 7.20-7.45 (5H, m), 7.7 (1H, ddd, J = 8.0, 2.0, 1.0 Hz), 7.8 (1H, m), 8.0 (1H, J = 1.8 Hz).

4-(3-bromo-phenyl)-5-methyl-oxazol-2-ylamine (216) and 5-(3-bromo-phenyl)-4-methyl-oxazol-2-ylamine (217)

A solution of 1-(3-bromo-phenyl)-2-hydroxy-propan-1-one and 1-(3-bromo-phenyl)-1-hydroxy-propan-2-one (2:1 mixture,

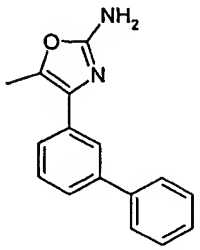
Compound 215, 18.8 g), cyanamide (10.4 g) and N,N-dimethylformamide (180 mL) was split equally between 40 microwave vials. The vessels were equipped with a stirrer bar, sealed with a crimped septum cap, and placed in the microwave cavity. The vials were heated at 200°C for 10 minutes, after this time the vials were allowed to cool to room temperature, and the resultant mixtures were combined in a round bottom flask, and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with 50 to 90 % ethyl acetate in dichloromethane to afford 4-(3-bromo-phenyl)-5-methyl-oxazol-2-ylamine (1.4 g, 7 %) as an orange solid. LC/MS System B: Rt = 4.74 min, m/z (ES^+) = 253, 255 ((M+H) for $C_{10}H_9BrN_2O$), ^1H NMR (DMSO-D6) 2.35 (3H, s), 6.5 (2H, br s), 7.3 (1H, t, J = 7.8 Hz), 7.4 (1H, ddd, J = 8.0, 2.1, 1.1 Hz), 7.5 (1H, m), 7.7 (1H, t, J = 1.8 Hz), then with 5 % methanol in dichloromethane to afford 5-(3-bromo-phenyl)-4-methyl-oxazol-2-ylamine (4.1 g, 20 %) as a cream solid. LC/MS System B: Rt = 4.55 min, m/z (ES^+) = 253, 255 ((M+H) for $C_{10}H_9BrN_2O$). ^1H NMR (DMSO-D6) 2.15 (3H, s), 6.8 (2H, br s), 7.3-7.4 (3H, m), 7.45 (1H, m).

Example 3(e): Synthesis of 4-biphenyl-3-yl-5-methyl-oxazol-2-ylamines



216 218

4-Biphenyl-3-yl-5-methyl-oxazol-2-ylamine, trifluoroacetic acid (218A)



In a microwave vial was placed 4-(3-bromo-phenyl)-5-methyl-oxazol-2-ylamine (Compound 216, 0.2 g), benzeneboronic acid (Compound 208A, 140 mg), palladium (0) tetrakis (triphenylphosphine) (36 mg), 2M cesium carbonate (1.6 mL), and N,N-dimethylformamide (2.4 mL). The vial was heated at 100°C for 3 minutes, allowed to cool to room temperature and then filtered through a short pad of hyflo. The filtrate was concentrated under reduced pressure and the residue was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford 4-biphenyl-3-yl-5-methyl-oxazol-2-ylamine, trifluoroacetic acid (22 mg, 8 %) as a pink solid. LC/MS System B: Rt = 5.41 min, m/z (ES^+) = 251 ((M+H) for $C_{16}H_{14}N_2O$). ^1H NMR ($CDCl_3$) 2.4 (3H, s), 7.35 (1H, m), 7.45-7.55 (4H, m), 7.6-7.7 (3H, m), 7.75 (1H, m).

Compounds 218B and 218C

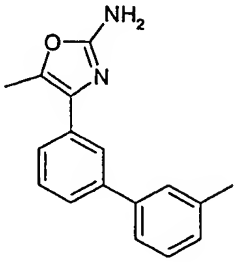
Similarly, replacing benzeneboronic acid (Compound 208A) with other compounds of formula (208):

3-methylbenzeneboronic acid (Compound 208B); and

2-methoxybenzeneboronic acid (Compound 208G);

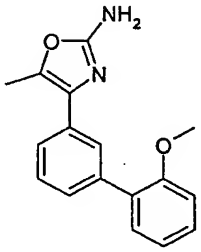
and following the procedures of preparation of Compound 218A above, the following compounds of the formula (218) were prepared:

5-Methyl-4-(3'-methyl-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (218B):



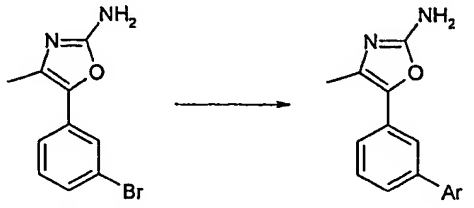
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (10 mg, 3 %) as a pink solid, LC/MS System B: Rt = 5.85 min, m/z (ES^+) = 265 ((M+H) for $C_{17}H_{16}N_2O$), ^1H NMR (DMSO-D6) 2.35 (3H, s), 2.40 (3H, s), 7.15 (1H, d, J = 7.5 Hz), 7.35 (1H, t, J = 7.5 Hz), 7.45-7.55 (4H, m), 7.6 (1H, m), 7.75 (1H, m).

4-(2'-methoxy-biphenyl-3-yl)-5-methyl-oxazol-2-ylamine, trifluoroacetic acid (218C):



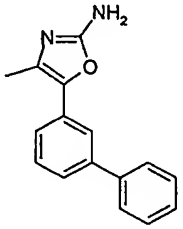
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (145 mg, 46 %) as a purple solid. LC/MS System B: Rt = 5.33 min, m/z (ES^+) = 281 ((M+H) for $C_{17}H_{16}N_2O_2$). ^1H NMR (DMSO-D6) 2.35 (3H, s), 3.75 (3H, s), 7.0 (1H, m), 7.1 (1H, d, J = 7.1 Hz), 7.3-7.5 (5H, m), 7.6 (1H, m).

Example 3(f): Synthesis of 5-biphenyl-3-yl-4-methyl-oxazol-2-ylamines



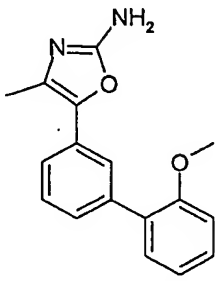
217 219

5-biphenyl-3-yl-4-methyl-oxazol-2-ylamine, trifluoroacetic acid (219A)



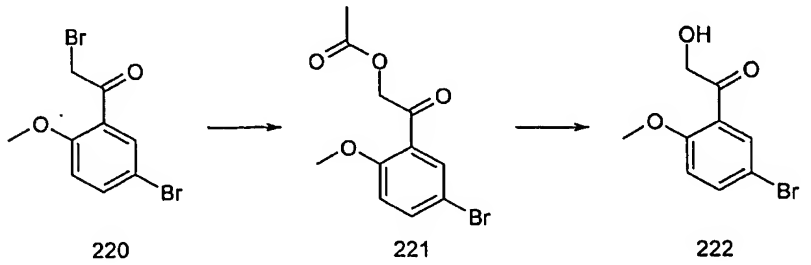
In a microwave vial was placed 5-(3-bromo-phenyl)-4-methyl-oxazol-2-ylamine (Compound 217, 0.2 g), benzeneboronic acid (Compound 208A, 140 mg), palladium (0) tetrakis (triphenylphosphine) (36 mg), 2M cesium carbonate (1.6 mL), and N,N-dimethylformamide (2.4 mL). The vial was heated to 100°C for 3 minutes, allowed to cool to room temperature and then filtered through a short pad of hyflo. The filtrate was concentrated under reduced pressure and the residue was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford 5-biphenyl-3-yl-4-methyl-oxazol-2-ylamine, trifluoroacetic acid (208 mg, 71 %) as a white solid. LC/MS System B: Rt = 5.34 min, m/z (ES^+) = 251 ((M+H) for $C_{16}H_{14}N_2O$). ^1H NMR (DMSO-D6) 2.3 (3H, s), 7.35 (1H, m), 7.4-7.5 (3H, m), 7.5-7.6 (2H, m), 7.60-7.65 (3H, m).

5-(2'-Methoxy-biphenyl-3-yl)-4-methyl-oxazol-2-ylamine, trifluoroacetic acid (219B)



Similarly, replacing benzeneboronic acid with 2-methoxybenzeneboronic acid (Compound 208G) and following the procedures of preparation of Compound 219A above, 5-(2'-methoxy-biphenyl-3-yl)-4-methyl-oxazol-2-ylamine, trifluoroacetic acid (153 mg, 49 %) was prepared as a white solid. LC/MS System B: Rt = 5.24 min, m/z (ES^+) = 281 ((M+H) for $C_{17}H_{16}N_2O_2$). ^1H NMR (DMSO-D6) 2.25 (3H, s), 3.75 (3H, s), 7.0 (1H, td, J = 7.5, 0.9 Hz), 7.1 (1H, d, J = 7.6 Hz), 7.3 (1H, dd, J = 7.6, 1.8 Hz), 7.3-7.4 (3H, m), 7.45-7.55 (2H, m).

Example 3(g): Synthesis of 5-(4-methoxy-biphenyl-3-yl)-oxazol-2-ylamines



Acetic acid 2 -(5-bromo-2-methoxy-pheny)-2-oxo-ethyl ester (221)

A mixture of 2-bromo-1-(5-bromo-2-methoxy-phenyl)-ethanone (Compound 220, 10.0 g), sodium acetate (2.7 g) and N,N-dimethylformamide (110 mL) was heated at 80°C for 2 hours. The N,N-dimethylformamide was removed under reduced pressure and the residue was partitioned between water (100 mL) and dichloromethane (100 mL). The organic layer was washed with water (100 mL), brine (100 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford acetic acid 2-(5-bromo-2-methoxy-pheny)-2-oxo-ethyl ester (9.2 g, 99 %) as a dark orange oil. ^{1}H NMR ($CDCl_3$) 2.15 (3H, s), 3.9 (3H, s), 5.15 (2H, s), 6.85 (1H, d, J = 8.8 Hz), 7.55 (1H, dd, J = 8.8, 2.6 Hz), 8.0 (1H, d, J = 2.6 Hz).

1-(5-Bromo-2-methoxy-phenyl)-2-hydroxy-ethanone (222)

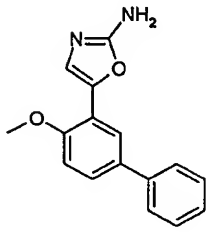
A mixture of acetic acid 2-(5-bromo-2-methoxy-pheny)-2-oxo-ethyl ester (Compound 221, 9.2 g) industrial methylated

spirits (50 mL) and 1 M hydrochloric acid (40 mL) was heated at reflux for 2 hours. The solvent was removed under reduced pressure and the residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was washed with water (50 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford 1-(5-bromo-2-methoxy-phenyl)-2-hydroxy-ethanone (6.5 g, 83 %) as a yellow solid. ^{1}H NMR ($CDCl_3$) 3.6 (1H, t, J = 4.8 Hz), 3.9 (3H, s), 4.7 (2H, d, J = 4.8 Hz), 6.85 (1H, d, J = 8.9 Hz), 7.6 (1H, dd, J = 8.9, 2.6 Hz), 8.1 (1H, d, J = 2.6 Hz).

5-(5-Bromo-2-methoxy-phenyl)oxazol-2-ylamine (223)

A solution of 1-(5-bromo-2-methoxy-phenyl)-2-hydroxy-ethanone (Compound 222, 6.5 g), cyanamide (3.3 g) and N,N-dimethylformamide (65 mL) was split equally between 13 microwave vials. The vessels were equipped with a stirrer bar, sealed with a crimped septum cap, and placed in the microwave cavity. The vials were heated at 200°C for 10 minutes, after this time the vials were allowed to cool to room temperature, and the resultant mixtures were combined in a round bottom flask, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with water water (100 mL), dried over magnesium sulfate and the solvent removed under reduced pressure to afford 4-(5-bromo-2-methoxy-phenyl)oxazol-2-ylamine (6.6 g , 65 %) as a dark orange solid. LC/MS System A: Rt = 2.26 min, m/z (ES^+) = 269, 271 ((M+H) for $C_{10}H_9BrN_2O_2$). ^{1}H NMR (DMSO-D6) 3.85 (3H, s), 6.9 (2H, br s), 7.0 (1H, d, J = 8.8 Hz), 7.1 (1H, s), 7.3 (1H, dd, J = 8.8, 2.4 Hz), 7.4 (1H, d, J = 2.4 Hz).

5-(4-methoxy-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (224A)



In a microwave vial was placed 5-(5-bromo-2-methoxy-phenyl)oxazol-2-ylamine (Compound 223, 200 mg), benzeneboronic acid (Compound 208A, 136 mg), palladium (0) tetrakis (triphenylphosphine) (34 mg), 2M cesium carbonate (1.5 mL), and dimethylformamide (3 mL). The vial was heated to 120°C for 3 minutes, allowed to cool to room temperature and then filtered through a short pad of hyflo. The filtrate was concentrated under reduced pressure and the residue was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford 5-(4-methoxy-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (32 mg, 11 %) as a white solid. LC/MS System B: Rt = 5.41 min, m/z (ES^+) = 267 ((M+H) for $C_{16}H_{14}N_2O_2$)

Compounds 224B and 224C

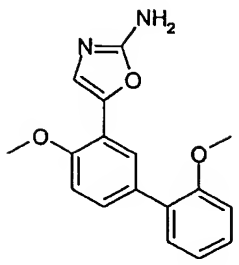
Similarly, replacing benzeneboronic acid (Compound 208B) with other compounds of formula (208):

2-methoxybenzeneboronic acid (Compound 208G); and

3-methylbenzeneboronic acid (Compound 208B)

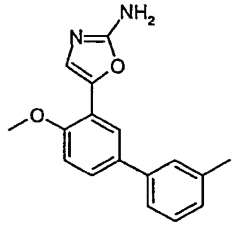
and following the procedures of preparation of Compound 224A above, the following compounds of the formula (224) were prepared:

5-(4,2'-dimethoxy-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (224B):



was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (29 mg, 10 %) as a white solid, LC/MS System B: Rt = 5.39 min, m/z (ES^+) = 297 ((M+H) for $C_{17}H_{16}N_2O_3$), ^1H NMR (DMSO-D6) 3.7 (3H, s), 3.9 (3H, s), 7.0 (1H, td, J = 7.4, 0.8 Hz), 7.05 (1H, d, J = 7.9 Hz), 7.1 (1H, d, J = 8.6 Hz), 7.2-7.3 (2H, m), 7.35-7.40 (2H, m), 7.55 (1H, m)

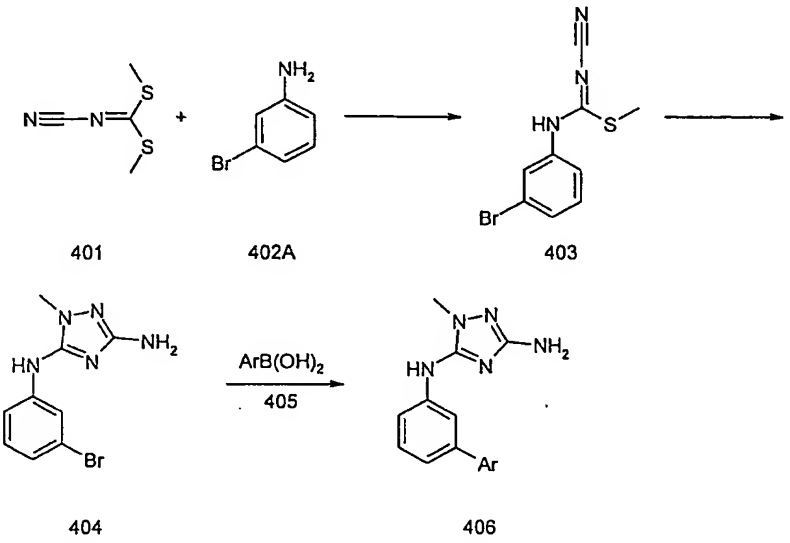
5-(4-Methoxy-3'-methyl-biphenyl-3-yl)-oxazol-2-ylamine, trifluoroacetic acid (224C):



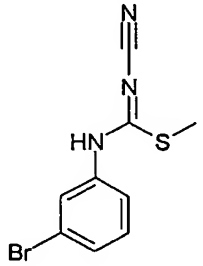
was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford the title compound (18 mg, 9 %) as an off-white solid, LC/MS System B: Rt = 2.71 min, m/z (ES^+) = 281 ((M+H) for $C_{17}H_{16}N_2O_2$), ^1H NMR (DMSO-D6) 2.35 (3H, s), 3.9 (3H, s), 7.1 (1H, d, J = 7.2 Hz), 7.2 (1H, d, J = 8.6 Hz), 7.3-7.4 (4H, m), 7.55 (1H, dd, J = 8.6, 2.4 Hz), 7.65 (1H, d, J = 2.2 Hz).

Example 4

Example 4(a): Synthesis of 1-methyl-N^5-biphenyl-1H-[1,2,4] triazole-3,5-diamines

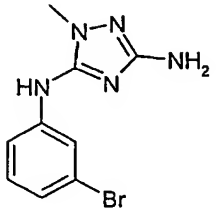


Methyl N'-cyano-N-(3-bromophenyl) carbamimidothioate (403)



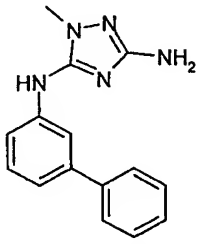
A mixture of dimethyl N-cyanodithioiminocarbonate (401, 10.0 g), 3-bromoaniline (402A, 5.6 g) and pyridine (50 mL) was heated at reflux for 3 hours. The solvent was removed under reduced pressure and the residue was washed with ethanol (200 mL) and diethyl ether (100 mL) to afford the title compound (5.4 g, 61%) as a white solid. ^{1}H NMR (DMSO-D6) 2.65 (3H, s), 7.3 (1H, t, J = 8.0 Hz), 7.40 (1H, m), 7.45 (1H, m), 7.65 (1H, t, J = 1.9 Hz).

N^5-(3-bromo-phenyl)-1-methyl-1H-[1,2,4]triazole-3,5-diamine (404)



A mixture of methyl *N'*-cyano-N-(3-bromophenyl) carbamimidothioate (403, 2.7 g), methylhydrazine (0.92 g) and butanol (10 mL) was heated at reflux for 2 hours. The solvent was removed under reduced pressure to give a yellow solid. The solid was recrystallised from ethyl acetate and washed with hexane to afford the title compound (1.5 g, 56 %) as a pale yellow solid. LC/MS System B: Rt = 2.33 min, m/z (ES^+) = 267 / 269 ((M+H) for $C_9H_{10}BrN_5$). ^1H NMR (DMSO-D6) 3.3 (3H, s), 5.05 (2H, br s), 6.95 (1H, m), 7.15 (1H, t, J = 8.1 Hz), 7.4 (1H, m), 7.85 (1H, t, J = 2.0 Hz), 8.8 (1H, br s).

N^5-biphenyl-3-yl-1-methyl-1H-[1,2,4] triazole-3,5-diamine (406A)



In a microwave vial was placed *N^5*-(3-bromo-phenyl)-1-methyl-1H-[1,2,4]triazole-3,5-diamine (404, 250 mg), benzeneboronic acid (Compound 405A, 170 mg), palladium (0) tetrakis(triphenylphosphine) (46mg), 2M cesium carbonate (1.5 mL), and N,N-dimethylformamide (2 mL). The vial was

heated to 100°C for 3 minutes, allowed to cool to room temperature and the solvent removed under reduced prsssure. The residue was dissolved in ethyl acetate and filtered through a short pad of hyflo to remove palladium residues. The filtrate was concentrated under reduced pressure and purified by column chromatography, eluting with 10% ethanol in ethyl acetate, to give a white solid. The solid was recrystallised from a mixture of ethyl acetate and hexane to afford the title compound (46 mg, 19 %) as a white solid. LC/MS System B: Rt = 2.62 min, m/z (ES^+) = 266 ((M+H) for $C_{15}H_{15}N_5$). ^1H NMR (DMSO-D6) 3.3 (3H, s), 5.0 (2H, br s), 7.1 (1H, m), 7.25-7.35 (2H, m), 7.4 (2H, m), 7.5-7.6 (3H, m), 7.75 (1H, t, J = 1.9 Hz), 8.65 (1H, br s).

Compounds 406B - 406C

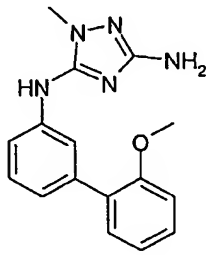
Similarly, replacing benzeneboronic acid with other compounds of formula (405):

2-methoxybenzeneboronic acid (Compound 405B);

3-methylbenzeneboronic acid (Compound 405C);

and following the procedures of preparation of 406A above, the following compounds of the formula (406) were prepared:

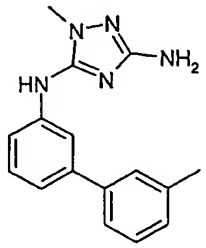
N^5-(2'-methoxy-biphenyl-3-yl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine (406B)



as a white solid (108 mg, 39 %); LC/MS System B: Rt = 2.57 min, m/z (ES^+) = 296 ((M+H) for $C_{16}H_{17}N_5O$), ^1H NMR (DMSO-D6) 3.25 (3H, s), 3.7 (3H, s), 4.95 (2H, br s), 6.9 (1H, m), 7.0

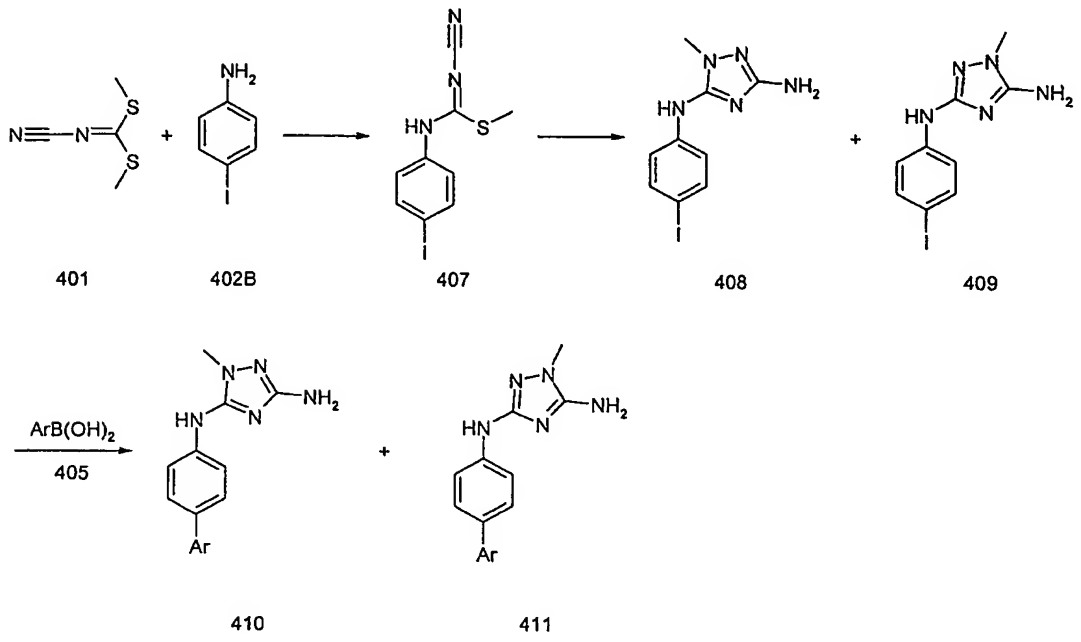
(1H, td, J = 7.4, 1.0 Hz), 7.05 (1H, m), 7.15-7.25 (2H, m), 7.3 (1H, m), 7.45 (1H, m), 7.55 (1H, t, J = 1.9 Hz), 8.6 (1H, br s).

1-methyl-N^5-(3'-methyl-biphenyl-3-yl)-1H-[1,2,4] triazole-3,5-diamine (406C)

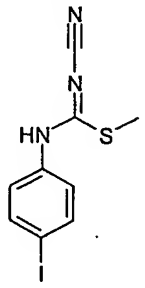


as a white solid (123 mg, 47 %), LC/MS System B: Rt = 2.81 min, m/z (ES^+) = 280 ((M+H) for $C_{16}H_{17}N_5$), ^1H NMR (DMSO-D6) 2.35 (3H, s), 3.25 (3H, s), 5.0 (2H, br s), 7.05-7.15 (2H, m), 7.25-7.40 (4H, m), 7.55 (1H, m), 7.7 (1H, t, J = 2.0 Hz), 8.6 (1H, br s).

Example 4(b): Synthesis of 1-methyl-N^3-biphenyl-1H-[1,2,4]triazole-3,5-diamines and 1-methyl-N^5-biphenyl-1H-[1,2,4]triazole-3,5-diamines



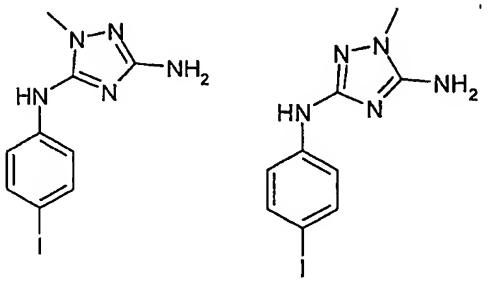
Methyl N'-cyano-N-(4-iodophenyl) carbamimidothioate (407)



A mixture of dimethyl *N*-cyanodithioiminocarbonate (401, 10.0 g), 4-iodoaniline (402B, 7.1 g) and pyridine (50 mL) was heated at reflux for 3 hours. The solvent was removed under reduced pressure and the residue was washed with industrial methylated spirits (300 mL) and diethyl ether (100 mL) to afford the title compound (6.9 g, 67%) as a white solid. ^{1}H NMR (DMSO-D6) 2.65 (3H, s), 7.25 (2H, m), 7.7 (2H, m), 10.1

(1H, br s).

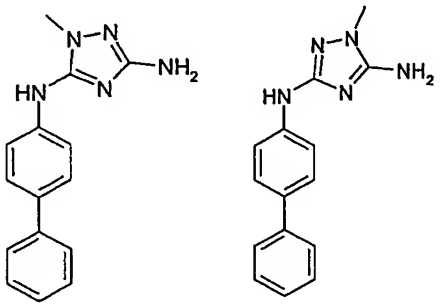
N^5-(4-iodo-phenyl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine (408) and N^3-(4-iodo-phenyl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine (409)



408 409

A mixture of methyl *N'*-cyano-N-(4-iodophenyl) carbamimidothioate (407, 3.0 g), methylhydrazine (0.87 g) and butanol (40 mL) was heated at reflux for 2 hours. The solvent was removed under reduced pressure to give a 2:1 mixture of N^5-(4-iodo-phenyl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine and N^3-(4-iodo-phenyl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine (3.1 g, 100 %) as a peach solid. A portion of the solid (100 mg) was purified by HPLC using a gradient of 20 to 80 % acetonitrile in water at 1 % per minute, to afford N^5-(4-iodo-phenyl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (59 mg, 59 %) as a white solid, LC/MS System B: Rt = 2.44 min, m/z (ES^+) = 316 ((M+H) for $C_9H_{10}IN_5$), ^1H NMR (DMSO-D6) 3.45 (3H, s), 7.3 (2H, m), 7.55 (2H, m), 9.0 (1H, br s) and N^3-(4-iodo-phenyl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (27 mg, 27 5) as a white solid, LC/MS System B: Rt = 2.49 min, m/z (ES^+) = 316 ((M+H) for $C_9H_{10}IN_5$), ^1H NMR (DMSO-D6) 3.4 (3H, s), 7.25 (2H, m), 7.5 (2H, m), 9.2 (1H, br s).

N^5-biphenyl-4-yl-1-methyl-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (410A) and N^3-biphenyl-4-yl-1-methyl-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (411A)



410A 411A

In a microwave vial was placed a 2:1 mixture of N^5-(4-iodo-phenyl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine and N^3-(4-iodo-phenyl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine (408 and 409, 200 mg), benzeneboronic acid (405A, 120 mg), palladium (0) tetrakis(triphenylphosphine) (29 mg), 2M cesium carbonate (1.3 mL), and N,N-dimethylformamide (2.5 mL). The vial was heated to 100°C for 3 minutes, allowed to cool to room temperature and filtered through a short pad of hyflo to remove palladium residues. The solvent was removed under reduced prsssure and the residue was purified by HPLC using a gradient of 20 to 80% acetonitrile in water at 1 % per minute, to afford N^5-biphenyl-4-yl-1-methyl-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (13 mg, 8 %) as an off-white solid, LC/MS System B: Rt = 2.64 min, m/z (ES^+) = 266 ((M+H) for $C_{15}H_{15}N_5$), ^{1}H NMR (DMSO-D6) 3.5 (3H, s), 7.25 (1H, m), 7.4 (2H, m), 7.5-7.6 (6H, m), 9.2 (1H, br s) and N^3-biphenyl-4-yl-1-methyl-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (8 mg, 5 %) as a white solid, LC/MS System B: Rt = 2.63 min, m/z (ES+) = 266 ((M+H) for $C_{15}H_{15}N_5$), ^{1}H NMR (DMSO-D6) 3.45 (3H, s), 7.25 (1H, m), 7.35 (2H, m), 7.5-7.6 (6H, m), 9.2 (1H, br s).

Compounds 410B - 410C and 411B - 411C

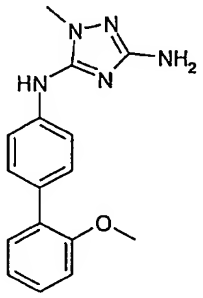
Similarly, replacing benzeneboronic acid with other compounds of formula (405):

2-methoxybenzeneboronic acid (Compound 405B);

3-methylbenzeneboronic acid (Compound 405C);

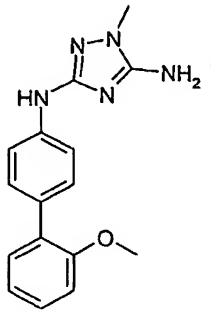
and following the procedures of preparation of 410A and 411A above, the following compounds of the formula (410) and (411) were prepared:

N^5-(2'-methoxy-biphenyl-4-yl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (410B)



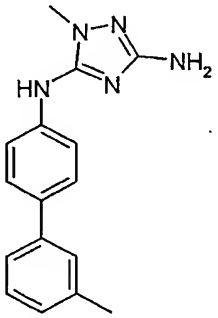
as a yellow solid (125 mg, 26 %), LC/MS System B: Rt = 2.61 min, m/z (ES^+) = 296 ((M+H) for $C_{16}H_{17}N_5O$), ^1H NMR (DMSO-D6) 3.5 (3H, s), 3.7 (3H, s), 6.95 (1H, td, J = 7.4, 1.1 Hz), 7.05 (1H, m), 7.2-7.3 (2H, m), 7.35-7.45 (4H, m), 9.2 (1H, br s).

N^3-(2'-methoxy-biphenyl-4-yl)-1-methyl-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (411B)



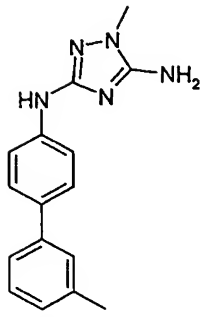
as a pale yellow solid (68 mg, 14 %), LC/MS System B: Rt = 2.59 min, m/z (ES+) = 296 ((M+H) for $C_{16}H_{17}N_5O$), ^{1}H NMR (DMSO-D6) 3.45 (3H, s), 3.7 (3H, s), 6.95 (1H, td, J = 7.4, 1.0 Hz), 7.0 (1H, m), 7.20-7.25 (2H, m), 7.30-7.35 (2H, m), 7.40-7.45 (2H, m), 9.25 (1H, br s).

1-methyl-N^5-(3'-methyl-biphenyl-4-yl)-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (410C)



as an off-white solid (17 mg, 4 %), LC/MS System B: Rt = 2.84 min, m/z (ES^+) = 280 ((M+H) for $C_{16}H_{17}N_5$), ^{1}H NMR (DMSO-D6) 2.3 (3H, s), 3.5 (3H, s), 7.1 (1H, m), 7.25 (1H, t, J = 7.6 Hz), 7.35-7.40 (2H, m), 7.45-7.55 (4H, m), 9.05 (1H, br s).

1-methyl-N^3-(3'-methyl-biphenyl-4-yl)-1H-[1,2,4] triazole-3,5-diamine trifluoroacetic acid (411C)



as an off-white solid (20 mg, 4 %), LC/MS System B: Rt = 2.80 min, m/z (ES^+) = 280 ((M+H) for $C_{16}H_{17}N_5$), ^1H NMR (DMSO-D6) 2.3 (3H, s), 3.45 (3H, s), 7.05 (1H, m), 7.25 (1H, t, J = 7.6 Hz), 7.35 (2H, m), 7.45-7.50 (4H, m), 9.2 (1H, br s).

Human cloned 5-HT_{2B} receptor binding assay

The binding affinity of the compounds for human cloned 5-HT_{2B} receptors was determined using the following assay.

CHO-K1 cells expressing cloned 5-HT_{2B} receptor were maintained in Ultra-CHO medium containing 400µg/ml of G418, 100U/ml penicillin, 100µg/ml streptomycin, 2.5µg/ml fungizone and 1% foetal bovine serum, in 95/5% O_2/CO_2 at 37°C. The cells were harvested using 0.25% trypsin and were centrifuged at 800rpm for 8 minutes. The cells were homogenised in 50mM HEPES buffer containing 1mM disodium EDTA and 1mM PMSF at pH 7.4, using a Dounce homogeniser (20 strokes). The homogenate was centrifuged at 2280rpm (1000g) and 4°C for 10 minutes, after which the supernatant was removed by decanting. The pellet was re-homogenised as above, and the resulting supernatant removed and combined with that already obtained. The supernatant solution was then centrifuged at 18300rpm (40000g) for 10 minutes at 4°C using a Sorvall centrifuge. The supernatant was removed, and the pellet was re-suspended in 50mM buffer at pH 7.4 using a Ultra-turrax T25 Polytron, before centrifugation again at

40000g as above. This wash procedure was repeated, after which the membrane preparation was stored at a concentration of 1mg/ml at -80°C until use.

The membranes were thawed rapidly and diluted in assay buffer containing Tris-HCl (50mM, pH 7.4), ascorbic acid (0.1%) and calcium chloride (4mM). The membranes were homogenised to resuspend them, prior to adding 10 or 15µg of membranes to assay wells containing [^{3}H]LSD (1nM), assay buffer (50mM Tris, 4mM calcium chloride and 0.1% ascorbic acid) containing pargyline (10µM), and the test compounds ($1x10^{-10}$ to $1x10^{-4}$M). Non specific binding was determined in the presence of 100µM 5-HT. After 30 minutes incubation at 37°C, the assay mixture was filtered through a combination of GF-C and GF-B filters, pre-soaked in 1% polyethyleneimine, using a Brandel cell harvester, and were washed three times using 50mM Tris-HCl. Radioactivity retained on the filters was determined by liquid scintillation counting. For each test compound, the concentration that inhibited binding of [^{3}H]LSD by 50% was determined using curve fitting software (Prism). Kd values (concentration of LSD required to occupy 50% of the receptor binding sites at equilibrium) determined from saturation binding studies were then used to calculate inhibition dissociation constants (Ki) using the following equation:

$$Ki = \frac{IC_{50}}{1 + \left(\frac{Radioligand\ concentration}{Radioligand\ Kd} \right)}$$

The results are shown in table 1 below as pKi values. This approach follows that set out in Kenakin, T.P. Pharmacologic analysis of drug-receptor interaction. Raven Press, New

York, 2nd Edition.

Human 5-HT_{2A} and 5-HT_{2C} receptor binding assays

The binding affinity of ligands for human 5-HT_{2A} and 5-HT_{2C} receptors was determined using the following assay. These results were then used to determine the selectivity of the test compounds for 5-HT_{2B} receptors, over 5-HT_{2A} and 5-HT_{2C} receptors.

Membrane preparations from CHO-K1 cells expressing the cloned human 5-HT_{2A} receptor were obtained (Euroscreen). The membranes were thawed rapidly and diluted in assay buffer containing Tris-HCl (50mM, pH 7.7). The membranes were resuspended by homogenisation, prior to adding 15µg of membranes to assay wells containing [3H] ketanserin (1nM), assay buffer (50mM Tris at pH 7.4) containing pargyline (10µM), and test compounds ($1x10^{-10}$ to $1x10^{-4}$M). Non specific binding was determined in the presence of 100µM mianserin. After 15 minutes incubation at 37°C, the assay mixture was filtered through a combination of GF-C and GF-B filters, pre-soaked in 0.05% Brij, using a Brandel cell harvester, and were washed three times using ice cold Tris-HCl buffer (50mM). Radioactivity retained on the filters was determined by liquid scintillation counting. For each test compound, the concentration that inhibited binding of [^{3}H]ketanserin by 50% was determined using curve fitting software (Prism). Kd values (concentration of ketanserin required to occupy 50% of the receptor binding sites at equlibrium)determined from saturation binding studies were then used to calculate inhibition dissociation constants (Ki) using the following equation:

$$Ki = \frac{IC_{50}}{1 + \left(\frac{Radioligand\ concentration}{Radioligand\ Kd} \right)}$$

Membrane preparations from CHO-K1 cells expressing the cloned human 5-HT_{2C} receptor were obtained (Euroscreen). The membranes were thawed rapidly and diluted in assay buffer containing Tris-HCl (50mM, pH 7.7), ascorbic acid (0.1%) and pargyline (10µM). The membranes were resuspended by homogenisation, prior to adding 6µg of membranes to assay wells containing [^{3}H] mesulergine (1nM), assay buffer (50mM Tris at pH 7.7 and 0.1% ascorbic acid) containing pargyline (10µM), and test compounds ($1x10^{-10}$ to $1x10^{-4}$M). Non specific binding was determined in the presence of 100µM mianserin. After 30 minutes incubation at 37°C, the assay mixture was filtered through a combination of GF-C and GF-B filters, pre-soaked in 1% bovine serum albumin, using a Brandel cell harvester, and were washed three times using ice cold Tris-HCl buffer (50mM). Radioactivity retained on the filters was determined by liquid scintillation counting. For each test compound, the concentration that inhibited binding of [^{3}H]mesulergine by 50% was determined using curve fitting software (Prism). Kd values (concentration of mesulergine required to occupy 50% of the receptor binding sites at equlibrium)determined from saturation binding studies were then used to calculate inhibition dissociation constants (Ki) using the following equation:

$$Ki = \frac{IC_{50}}{1 + \left(\frac{Radioligand\ concentration}{Radioligand\ Kd} \right)}$$

The results are shown in table 1 below as pKi values.

Table 1

Compound	5-HT_{2B}	5-HT_{2A}	5-HT_{2C}
2A	>6	<5	<6
2E	>6	<5	<6.5
2F	>6	<5	<5
2G	>7	<5.5	<6.5
2H	>6	<5	<6
2I	>6	<5	<6
2J	>7	<5	<6
2K	>6	<5	<5
2M	>6	<6	<6
2N	>6	<6	<6
2O	>6	<6	<7
2Q	>6	<6	<6
2R	>6	<6	<6
2S	>7	<6	<6.5
2T	>6	<6	<6
2U	>6	<6	<6
2V	>6	<6	<6
2X	>6	<6	<6
2Y	>7	<6	<6
2AB	>6	<6	<6
2AC	>6	<6	<6
2AD	>6	<6.5	<6
2AE	>7	<5	<6.5
2AF	>6	<5.5	<6
2AJ	>7	<6	<6.5
2AK	>7	-	-
2AN	>6	<5	<6
2AP	>6	<6	<6
4B	>7	<5	<5

4C	>6	<5	<5
10A	>7	<7	<6.5
10B	>6	<5	<5
10C	>6	<6.5	<6.5
10D	>6	<6	<6
10E	>7	<7	<7
10F	>7	<6.5	<7
10G	>7	-	-
10H	>7	<6.5	<6.5
10I	>6	<5	<5
11A	>8	<6	<7
11B	>8	<6	<7.5
12	>7	<6	<6
16	>6	<6	<6
103A	>7	<5.5	<6
103B	>6	<5	<5
103C	>7	<6.5	<6.5
103E	>7	<5	<6
103F	>7	<5.5	<5.5
103G	>7	<6	<6
103H	>7	<6	<6
103I	>7	<6	<6
103L	>7	<5	<5
103N	>6	<5	<5
103O	>6	<5	<5
103Q	>6	<5.5	<6
104A	>6	<6	<7
104B	>7	<5.5	<5.5
104C	>7	<6	<6.5
104D	>6	<6.5	<6
104E	>7	<6	<7
104F	>7	<6	<6

104G	>7	<6.5	<6.5
104H	>7	<6.5	<7
104I	>7	<5.5	<6
104J	>7	<6.5	<7
104K	>7	<7	<6.5
104O	>6.5	<5	<6.5
104P	>6.5	<7	<6.5
107	>6	-	-
108	>7	<6.5	<7
209A	>6.5	<5	<5
209B	>6.5	<5	<5
209C	>6	<5	<5
209E	>6.5	<6	<5
209G	>7	<6	<6
209J	>6	<6	<6
209K	>6	<6	<6
209M	>6	-	-
218A	>6	<6	<6
218B	>6	-	-
218C	>6.5	<6	<6
219A	>6.5	<6	<6
219B	>7	<6	<6
224A	>6	<6	<6
224B	>6.5	<6	<6
224C	>6	<6	<6
406A	>6.5	<6	<6
406B	>6.5	<6	<6
406C	>7	<6	<6
410C	>6	<6	<6
411A	>6	<6	<6
411B	>6	<6	<6
411C	>6	<6	<6

Human cloned 5-HT_{2B} cell-based functional assay

The following describes an *in vitro* functional assay using human cloned 5-HT_{2B} receptors to determine the ability of compounds to block the receptor.

CHO.K1 cells expressing cloned 5-HT_{2B} receptor were maintained In Ultra-CHO medium containing 400µg/ml of G418, 100U/ml penicillin, 100µg/ml streptomycin, 2.5µg/ml fungizone, in 95/5% O_2/CO_2 at 37°C. Ultra-CHO medium additionally supplemented with 1% foetal bovine serum was used when seeding the cells and removed after 5 hours. Cells were plated in Costar 96 well white, clear-bottomed plate at a density of 50,000 cells per well and incubated for at least 24 hours in 95/5% O_2/CO_2 at 37°C before running the assay.

Media was removed from the wells and 200µl of 4µM Fluo-4 AM added, this was incubated in a Wallace Victor 2V workstation at 37°C for 30 minutes. The Fluo-4 AM was then removed from the wells, which were then washed twice with 200µl of buffer (HBSS without calcium/magnesium/phenol red, 20mM HEPES, 1mM Ca^{2+}, 1mM Mg^{2+}, 2.5mM probenecid, pH to 7.4), 180µl of buffer or test compound was added to the well and incubated for 30 minutes. The Victor 2V injectors were used to inject 20µl of 5-HT after obtaining 10 0.1-second baseline readings at 535nm, followed by 150 readings.

All test compounds were aliquoted in 100% DMSO at 10mM and diluted to 1mM in 50% DMSO, subsequent dilutions were made using buffer. Buffer was also used to dilute the 5-HT. Data were analysed using Microsoft Excel and GraphPad Prism, with the latter used to produce sigmoidal dose-response

curves for each compound. The compound concentration that inhibited the 5-HT response by 50% was taken (IC_{50} - M), and the results are shown in Table 2, as pIC_{50}, being the negative log (to the base 10) of the measured IC_{50} values.

Table 2

Compound	pIC_{50}
103C	>7
103F	>7
104C	>6
104J	>7
219B	>6
406C	>7